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PELVIC MODEL MANIKINS TO SHOW PELVIC SHAPE AND TO DEMONSTRATE LABOR MECHANISMS*

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THE obstetrical manikin in its simplest form consists of an articulated pelvis and an artificial fetal head. The success of this method of teaching suggested the development of a series of models showing the classical and mixed inlet types previously described in detail,[1, 2, 3] and the common variations in the mid and lower pelvis. It was considered mechanically possible to design each model for use as a manikin to demonstrate the influence exerted by pelvic shape upon head position and the common manual and forceps mechanisms. This objective has been obtained and the present presentation deals with the description, source of material and use of sixteen pelvic model manikins designed for teaching purposes.

Design and Use of Models

The series consists of sixteen models, fourteen showing pure and mixed pelvic types; one a male pelvis, and one an asymmetrical example.

Each model is made in a durable plastic material and is fixed to a solid metal base, supported by an adjustable U-shaped upright (Fig. 1). In this position, the student can inspect the pelvis and study its morphologic characteristics through the inlet, from the lateral aspect and through the subpubic arch. By adjustment of screws, A and B (Fig. 1) each model is converted into a fixed rigid manikin, Fig. 2.

The metal base is not essential if these models are kept permanently in a special manikin room. In this event the sixteen specimens can be displayed on a long table with the base support of the U-shaped

*This study has been made possible by a grant from the Commonwealth Fund.

upright (Fig. 1C) permanently fixed to the table top. When it is necessary to use any model as a manikin the screws A and B (Fig. 1) are adjusted to bring the sacral tip to the edge of the table holding it rigidly as shown in Fig. 2.

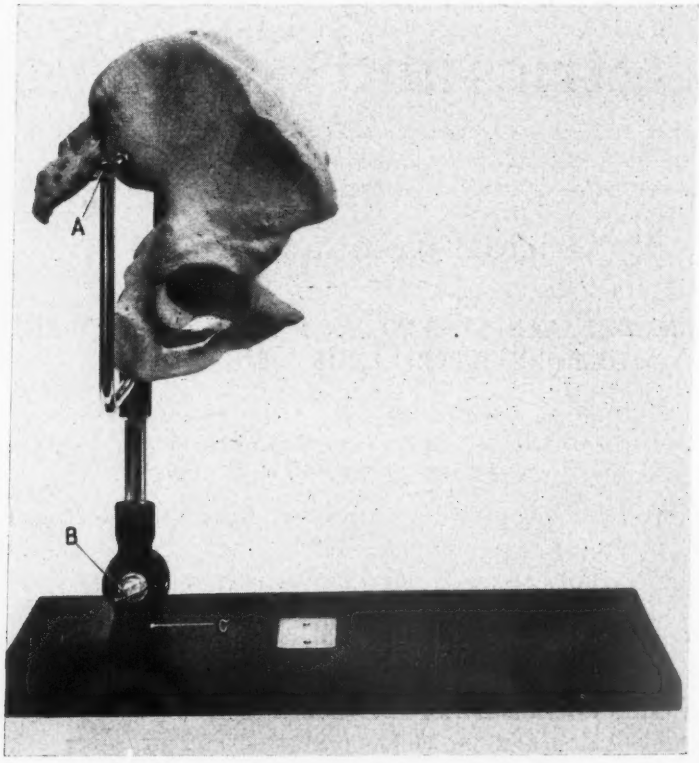

Fig. 1.—Model supported by U-shaped upright and fixed to a solid base in position for study of pelvic morphology. Screws A and B are adjustable. The metal base is not essential and joint C may be fixed permanently to any suitable manikin table.

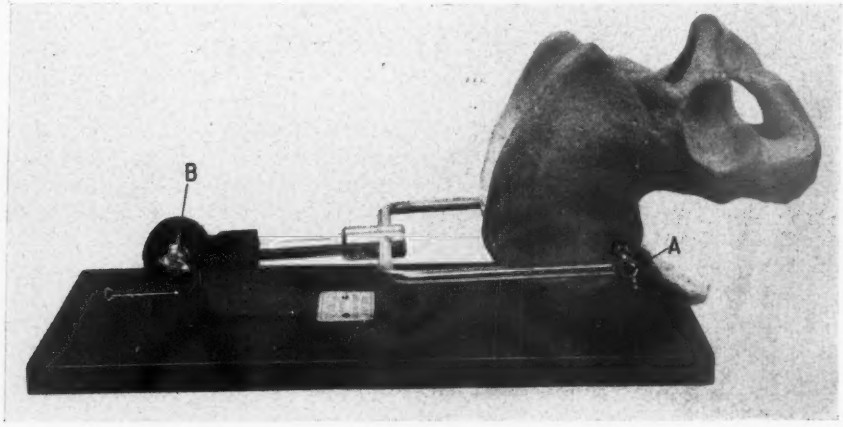

Fig. 2.—By adjustment of screw A and B, the pelvic model is converted into a rigid manikin.

Source of Material

The original pelves from which these models were constructed were selected from the well-known collection of the late Dr. T. Wingate Todd, Western Reserve University, Cleveland. This collection is unique in many ways. The sex of each skeleton is known, as well as the race and approximate age; also, in many instances, a brief medical history and photograph of the cadaver exists. Dr. Todd recorded the significant anthropometric measurements before maceration including the anteroposterior and transverse diameter of the inlet. The size of the collection is in itself important (over 800 female pelves) as it allows the observer greater choice of individual types.

Late in 1942, Dr. Normand Hoerr, head of the Department of Anatomy, Western Reserve University, became acquainted with this project and granted permission to visit his laboratory and examine, once again, the Todd skeletal material. Dr. W. W. Greulich, in the absence of Dr. Hoerr, extended every courtesy, demonstrated an interest in the grouping of these pelves according to type and approved the examples which were ultimtaely chosen for this series.

A Brief Description of Classification

The method of inlet classification used in the selection of these teaching models is diagrammatically illustrated in Fig. 3. In Fig. 3, A to D, the shape of the anterior and posterior segments of the four pure types is shown. Mixed forms are quite numerous and are classified according to the theory that mixed forms, in shape, appear to represent the fusion of a posterior segment of one pure type with an anterior segment of another pure form (Fig. 3, E to N). Theoretically, twelve mixed types occur, but the two anthropoid-flat combinations have not as yet been recognized. In the scheme of terminology for mixed types, the first term refers to the posterior segment and the second term to the anterior segment.

The pathologic types listed in the latest edition of Stander's revision of Williams' Textbook have been added to the morphologic classification under appropriate subdivisions.

Classification of Pelves*

I. NORMAL FEMALE GROWTH TYPES.

A. Variation at the inlet:

1. True anthropoid type.
2. Anthropoid-gynecoid type.
3. Anthropoid-android type.
4. True gynecoid type.
5. Gynecoid-anthropoid type.
6. Gynecoid-android type.
7. Gynecoid-flat type.
8. True android type.

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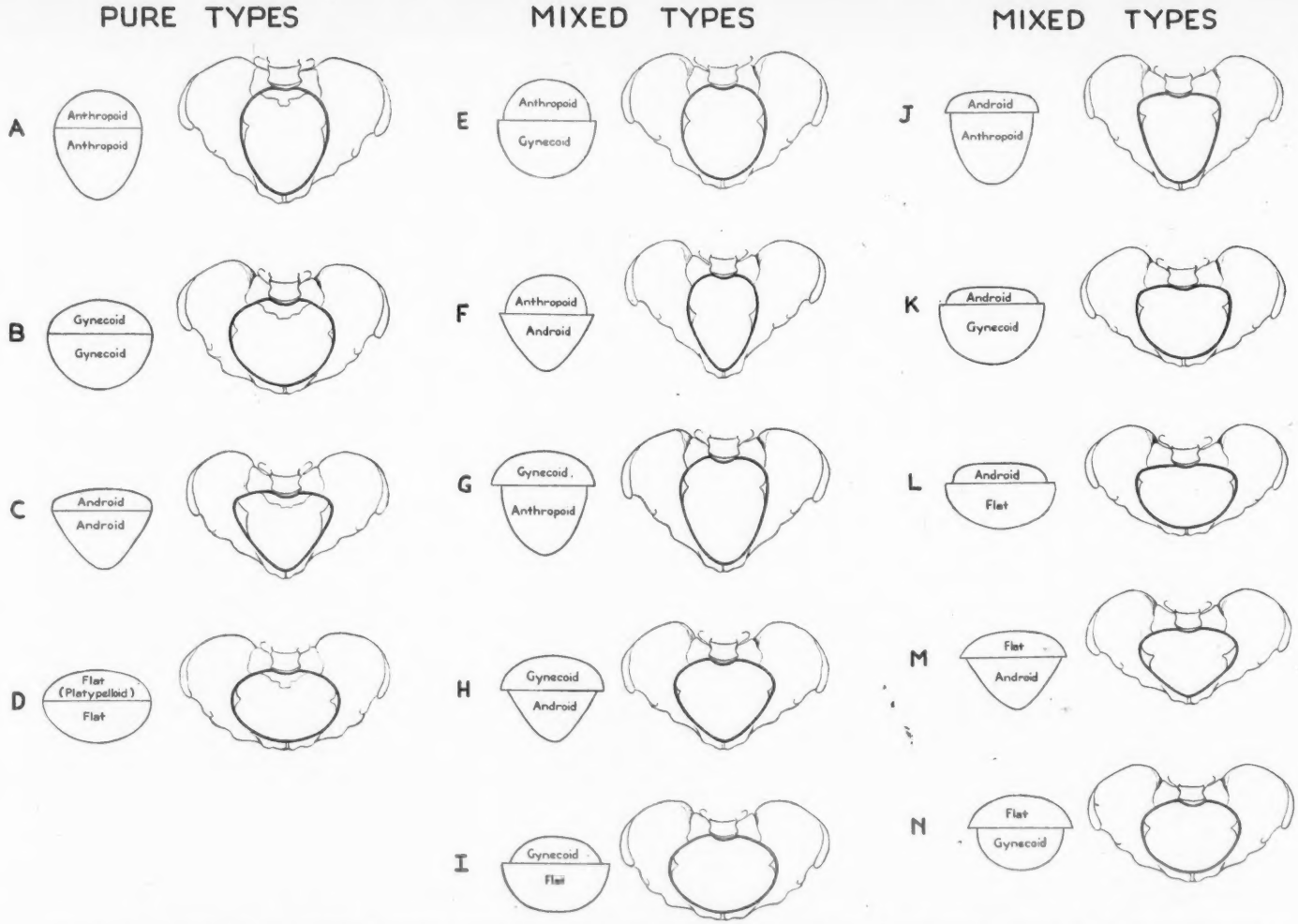


Fig. 3.—The principle of combining pelvic segments to classify the mixed inlet types. Pure types have a characteristic shape to the anterior and posterior segments (A-D). Mixed forms are classified by the combination of segments. The first term of a combination designates the posterior segment, the second term the anterior segment. *A*, Pure anthropoid; *B*, pure gynecoid; *C*, pure android; *D*, pure platypelloid (flat); *E*, anthropoid-gynecoid (mixed); *F*, anthropoid-android (mixed); *G*, gynecoid-anthropoid (mixed); *H*, gynecoid-android (mixed); *I*, gynecoid-flat (mixed); *J*, android-anthropoid (mixed); *K*, android-gynecoid (mixed); *L*, android-flat (mixed); *M*, flat-android (mixed); *N*, flat-gynecoid (mixed).

9. Android-anthropoid type.
10. Android-gynecoid type.
11. Android-flat type.
12. True platypelloid type.
13. Flat-gynecoid type.
14. Flat-android type.

B. Variations below the inlet:

1. Side walls of pelvis ---------- divergent, straight, or convergent.
2. Subpubic arch ---------- wide, moderate, narrow.
3. Pubic rami ---------- straight (masculine or Gothic), curved (feminine or Norman).
4. Pubic symphysis ---------- masculine or feminine type.
5. Ischial spines ---------- long, sharp, short, or flat.
6. Apex of sacrosciatic notch ---------- wide, average, narrow.
7. Base of sacrosciatic notch ---------- wide, average, narrow.
8. Number of sacral segments.
9. Sacral curvature ---------- (a) longitudinal—straight, average, marked.
   (b) transverse—straight, average, marked.
10. Sacral inclination ---------- (a) upper portion—forward, average, backward.
    (b) lower portion—forward, average, backward.
11. Terminal sacrum ---------- sharp, average, blunt.
12. Lateral bore ---------- divergent, straight, convergent.

C. General pelvic variations:

1. Pelvic size ---------- (a) large, average, small.
   (b) pelvimetry measurements of cardinal diameters.
2. Pelvic bones ---------- heavy, average, light.
3. Symmetry of pelvis ---------- (a) symmetrical at inlet, mid, or lower pelvis.
   (b) asymmetrical (to right) at inlet, mid or lower pelvis.
   (c) asymmetrical (to left) at inlet, mid, or lower pelvis.

II. ABNORMAL GROWTH AND DEVELOPMENTAL TYPES.

(In addition to the abnormality, the pelvis may be classified morphologically as outlined in Group I.)

1. Infantile.
2. Dwarf.

III. TYPES CAUSED BY DISEASE OF THE PELVIC BONES AND JOINTS.

(In addition to the abnormality, the pelvis may be classified morphologically as outlined in Group I.)

A. Metabolic:

1. Rachitic:
   a. Flat.
   b. Generally contracted and flat.
   c. Generally contracted.
2. Osteomalacic.

combination designates the platypelloid (flat); *E*, anthropoid-gynecoid (mixed); *F*, android-anthropoid (mixed); *G*, pure android; *D*, pure platypelloid (flat); *E*, anthropoid-gynecoid (mixed); *I*, gynecoid-flat (mixed); *J*, android-anthropoid (mixed); *K*, gynecoid-android (mixed); *H*, flat-android (mixed); *M*, flat-gynecoid (mixed); *L*, android-flat (mixed).

B. Congenital, inflammatory, and atypical types:

1. Assimilation pelvis.
2. Split pelvis.
3. Naegele's pelvis.
4. Robert's pelvis.
5. Coxalgic.
6. Coxarthrolisthetic.
7. Pelvis spinosa.
8. Neoplastic.

C. Traumatic types:

1. Fracture of pelvis.
2. Separation of symphysis.

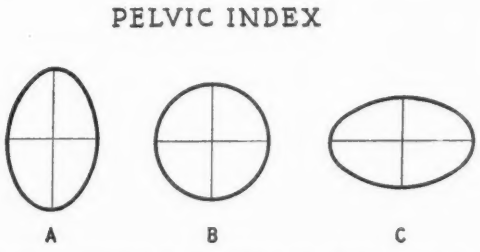


Fig. 4.—The pelvic index reveals a transition in shape from a longitudinal ellipse through a round form to a transverse ellipse, *A*, *B*, *C*.

IV. TYPES SECONDARY TO ABNORMALITIES IN THE SPINAL COLUMN.

(In addition to the abnormality, the pelvis may be classified morphologically as outlined in Group I.)

1. Kyphotic pelvis.
2. Kyphorachitic pelvis.
3. Scoliotic pelvis.
4. Kyphoscoliotic pelvis.
5. Kyphoscoliorachitic pelvis.
6. Spondylolisthetic pelvis.

V. TYPES SECONDARY TO ABNORMALITIES OF THE LOWER EXTREMITIES.

(In addition to the abnormality, the pelvis may be classified morphologically as outlined in Group I.)

1. Luxation of femora.
2. Atrophy or loss of one or both extremities.

A careful study will show that there are at least five factors to consider in devising a classification of pelves sufficiently comprehensive to describe the pelvis as a whole from inlet to outlet.

First.—The classification must take into account the so-called pelvic index which concerns the relationship of the length of the anteroposterior diameter of the inlet to the widest transverse diameter of the inlet. This index reveals a transition in shape from the extreme long narrow oval through the round to the flat or transverse oval shape.

(Fig. 4.) This transition in shape may be demonstrated in the pelvic models if the observer studies the inlet views of the following types in series: anthropoid-android, anthropoid, anthropoid-gynecoid, gynecoid-anthropoid, gynecoid, gynecoid-flat, flat-gynecoid and the typical platypelloid type. Individual pelves in the above series may show variations not indicated by the pelvic index. This observation introduces the second and third factors to consider in this classification.

Second.—There is individual variation in the shape of the posterior segment of the inlet. The widest transverse diameter divides the pelvis into an anterior and posterior segment and the point of intersection of this diameter with the anteroposterior diameter forms the anterior and posterior sagittal diameter at the inlet. Variations in the position of the widest transverse diameter effects equal variations in the lengths of these inlet sagittal diameters. Four characteristic types of posterior segments can be recognized and are illustrated diagrammatically in Fig. 5. These are the posterior segments of the "anthropoid," "gynecoid," "android," and "platypelloid" pelvic types. It may be pointed out that there are intermediate forms of posterior segments between the four classical shapes illustrated in Fig. 5. Experience has shown that these four posterior segment shapes are quite adequate for classification purposes.

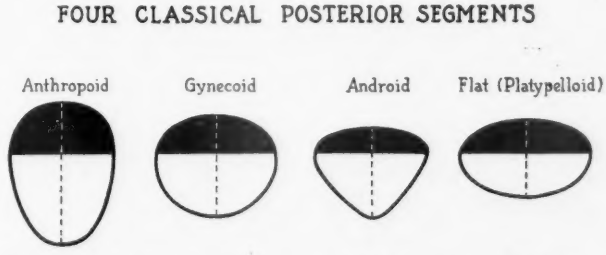


Fig. 5.—The pelvic index does not consider the relationship of the widest transverse diameter of the inlet to the anteroposterior diameter. In the classic or pure types the point of intersection produces variable posterior and anterior sagittal diameters with a typical posterior segment for each type.

Third.—This factor deals with the variations in the anterior segment. The four classical or pure pelvic types of course, possess characteristic anterior segments which are termed "*anthropoid,*" "*gynecoid,*" "*android,*" and "*flat*" (platypelloid). (Fig. 6.) Intermediate shapes between those classical types also occur in the anterior segment, and their classification may afford difficulty to the inexperienced observer unless the trend in forepelvic variations is understood. The factors which modify the shape of the anterior segment at the inlet appear to resemble in overlapping of sexual characteristics (Fig. 6A). Female characters produce a well-formed wide anterior segment with good curvature to the iliopectineal lines radiating from the symphysis. (Fig. 6B.) Male characters produce a narrow angular anterior segment with straight iliopectineal lines deviating backward from the symphysis. (Fig. 6C.) Lack of curvature in the side walls of the anterior segment at the inlet is considered in itself, a masculine character and gives a characteristic angular or wedge-shaped appearance without regard to the size of the retropubic angle. Thus an "android" anterior segment may be "narrow," "average," or "wide," providing the lateral borders are straight enough to produce an angular shape. (Fig. 6C.) This explains

why the term "flat android" is used to designate a flat pelvis with a blunt wedge-shaped appearance, or why the term "anthropoid-android" is used to define an anthropoid pelvis with a narrow forepelvis. If the forepelvis has a long anterior sagittal diameter, it may be termed "anthropoid," as is used in the "android-anthropoid" type.

The anthropoid, gynecoid and flat anterior segments, in classical types, are well formed and female in shape (Fig. 6A) and the differences in these types concern chiefly the size of the retropubic angle and, to a lesser extent, the length of the anterior sagittal diameter. Steele and Javert[4] have recently described the "anterior transverse diameter" through the forepelvis which, when compared to the widest transverse diameter, gives a linear expression of the curvature present in the forepelvis which is an aid in the recognition of the android anterior segment.

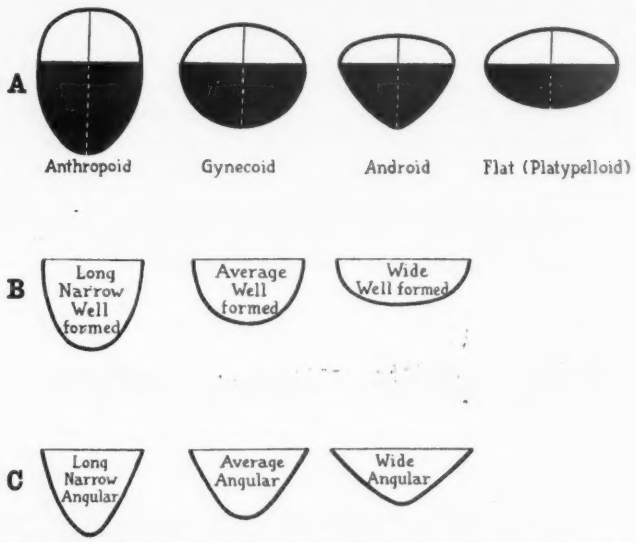


Fig. 6.—Factors affecting shape in the anterior segment. *A*, The classical shape for the anthropoid, gynecoid, android, and flat anterior segments; *B*, the appearance of female characteristics associated with narrow, moderate, and wide retropubic angles; *C*, the appearance of male characteristics associated with narrow, moderate, and wide retropubic angles.

Fourth.—Variations in the side walls, sacral curvatures and inclinations, size and shape of the subpubic arch, number of sacral segments and other features must be expressed by an appropriate terminology. A complete list of terms is outlined in the formal classification.

Fifth.—There are a number of variable factors that affect the pelvis as a whole and these, including the lengths of the cardinal pelvic diameters, are listed in the formal classification.

Selection of Typical Types for Teaching Models

From the information listed in the history associated with each skeleton in Todd's collection, it is possible to divide the pelves into two racial groups—white and Negro. It is admitted, however, that the American Negro is no longer a pure racial type. The white race also shows great racial intermixture. In the work associated with the selection of suitable pelvic types, two long tables were used—one for

the white group and one for the so-called Negro group. Each individual pelvis was classified according to the principles outlined in the formal classification. Slowly, as more pelves were examined and classified, fourteen collections of pelves accumulated on each table, totaling approximately three hundred pelves.

During the process of typing this large series of skeletal pelves, several interesting observations were made. It was noted that in pelves which demonstrated marked convergence of the side walls, the inlet usually revealed a long oval or anthropoid tendency. A number of excellent android types were found with a characteristic wedge-shaped inlet but, as a rule these examples showed straight side walls with an ample subpubic arch or some other variations from the classical android form. The pelves showing a characteristic masculine posterior segment, frequently revealed a forepelvis which was too well formed to select as a typical android type. This fact is noted in the excellent android-gynecoid type finally chosen for the teaching series (Fig. 7K). For these reasons, the android example which was selected to show convergence of the side walls and a narrow subpubic arch, has a longer anteroposterior diameter than is found in the classical or pure android type. The selected example (Fig. 7C), therefore, does not appear to show the characteristic flat posterior segment of a typical android. Careful examination of this specimen reveals that the apparently ample appearance of this posterior segment is caused by the transverse or coronal curvature in the first sacral segment. The notch is quite masculine at the apex and the section of the ilium over the apex of the notch is characteristically short.

Difficulty was encountered in the classification of the mixed anthropoid-gynecoid types and the gynecoid-flat forms. Many mixed anthropoid types, i.e., gynecoid-anthropoid and anthropoid-gynecoid types, were found and it was difficult to determine whether certain individual pelves belonged in one or the other mixed group. The key-diagram shown in Fig. 3, is a great aid in the classification of these doubtful examples. Individual observers might disagree in the typing of these indeterminate types but an error in typing is not serious as long as the pelvis is recognized as of a shape intermediate between the classical anthropoid and gynecoid forms. The same difficulty was found in the classification of "gynecoid-flat," and "flat-gynecoid" combinations. Here again, if attention is paid to the position of the widest transverse diameter and its point of intersection on the anteroposterior diameter, these mixed flat types can be classified into their correct group without too much difficulty.

This discussion of the practical difficulties encountered in selecting a series of skeletal pelves from which to make a set of teaching models illustrates that individual pelves show many minor characteristics which either cannot be classified or which detract from the classical

prototype. Of course this observation is not unexpected when dealing with anatomic material. A teaching series of models could be developed by a good sculptor, who understood the anatomic significance of the shapes of the prototypes illustrated in Fig. 3. It would be quite possible for him to add the common variations in the mid and lower pelvis which are outlined in the formal classification. However, after granting this possibility, it is felt that models made from actual skeletal material, have greater value for teaching purposes, because they show the combination of variations which can be expected in living patients.

The frequency of occurrence of the fourteen pelvic types, for each race is of interest. The same trend indicated in Table I was also noted in our original study of this same material in 1933, at which time, the pelves were classified into the four classical types, i.e., anthropoid, gynecoid, android and platypelloid.

TABLE I. FREQUENCY OF OCCURRENCE

	WHITE RACE		NEGRO RACE	
	NUMBER	PER CENT	NUMBER	PER CENT
Anthropoid	6	5	14	8.1
Anthropoid-gynecoid	7	5.8	21	12.2
Gynecoid-anthropoid	6	5	27	15.7
Anthropoid-android	6	5	7	4.1
Android-anthropoid	3	2.5	2	1.2
Android	4	3.3	5	3
Gynecoid-android	13	10.8	22	12.9
Android-gynecoid	6	5	7	4.1
Gynecoid-flat	3	2.5	1	0.6
Flat-gynecoid	4	3.3	1	0.6
Android-flat	3	2.5	1	0.6
Flat-android	2	1.6	3	1.7
Flat	2	1.6	1	0.6
Gynecoid	55	45.8	60	34.9
Total	120		172	

The Negro race shows a higher incidence of anthropoid and anthropoid-mixed types. The white race shows a slightly higher incidence of flat, mixed-flat, and android types than the Negro race.

Description of Pelvic Models

The Anthropoid-Android Type.—Fig. 7F (Prototype Fig. 3F). Western Reserve No. 3210, Negro.

This is an unusually fine example of an anthropoid-android type. The long narrow anterior segment gives to the pelvic inlet a more extreme long oval appearance than is noted in the classical anthropoid type. This particular example is ideal to use in demonstrating the extreme anthropoid characters and the classical posterior mechanism which is common to the anthropoid and related mixed types.

The narrow forepelvis increases the possibility of a posterior mechanism because the narrow anterior segment receives the frontal region of the head more readily than the rounded occiput. For this reason the anthropoid type with a narrow forepelvis should be distinguished from the typical anthropoid pelvis with a well-formed forepelvis in which an-

terior oblique positions occur more frequently than posterior positions. Hence, this particular mixed type is correctly classified as an "anthropoid-android" mixed form.

The Anthropoid Type. Fig. 7A (Prototype Fig. 3A). Western Reserve No. 2172, Negro.

In order to emphasize the characters of the anthropoid-android type just described, it is necessary, for contrast, to select the classical anthropoid example to show a well-formed long narrow oval shape. Certain observers may contend that this particular example is too gynecoid in appearance to represent the classical anthropoid form, and may consider it more characteristic of a gynecoid-anthropoid or anthropoid-gynecoid mixed type. However, to select a narrower long oval than the example shown, would tend to place the pelvis in the anthropoid-android group. The actual specimen shows more anthropoid characters than is indicated in the photograph of the model as shown in Fig. 7A.

Anthropoid-Gynecoid Type.—Fig. 7E (Prototype Fig. 3E). Western Reserve No. 2116, Negro.

This type and the gynecoid-anthropoid mixed form are quite similar in general inlet shape. The classical differences are indicated to better advantage in the prototypes Fig. 3 E and G. The chief differences exist in the position of the widest transverse diameter and the point of intersection on the anteroposterior diameter. The anthropoid-gynecoid type has a very wide sacrosciatic notch with a very long segment of ilium over the apex of the notch between the point of origin of the widest transverse diameter and the sacroiliac synchondrosis. This feature may be emphasized by the presence of a transverse sacral curvature in the first sacral segment.

Gynecoid-Anthropoid Type.—Fig. 7G (Prototype Fig. 3G). Western Reserve No. 715, White.

In this example the posterior segment has a flat appearance because the sacrosciatic notch is not so wide as in the anthropoid-gynecoid type and the section of ilium at the apex of the notch is not as long. The anthropoid appearance may result from slight narrowing of the retropubic angle of the anterior segment behind the symphysis. This particular example was also selected to show a markedly forward lower sacrum with six sacral segments.

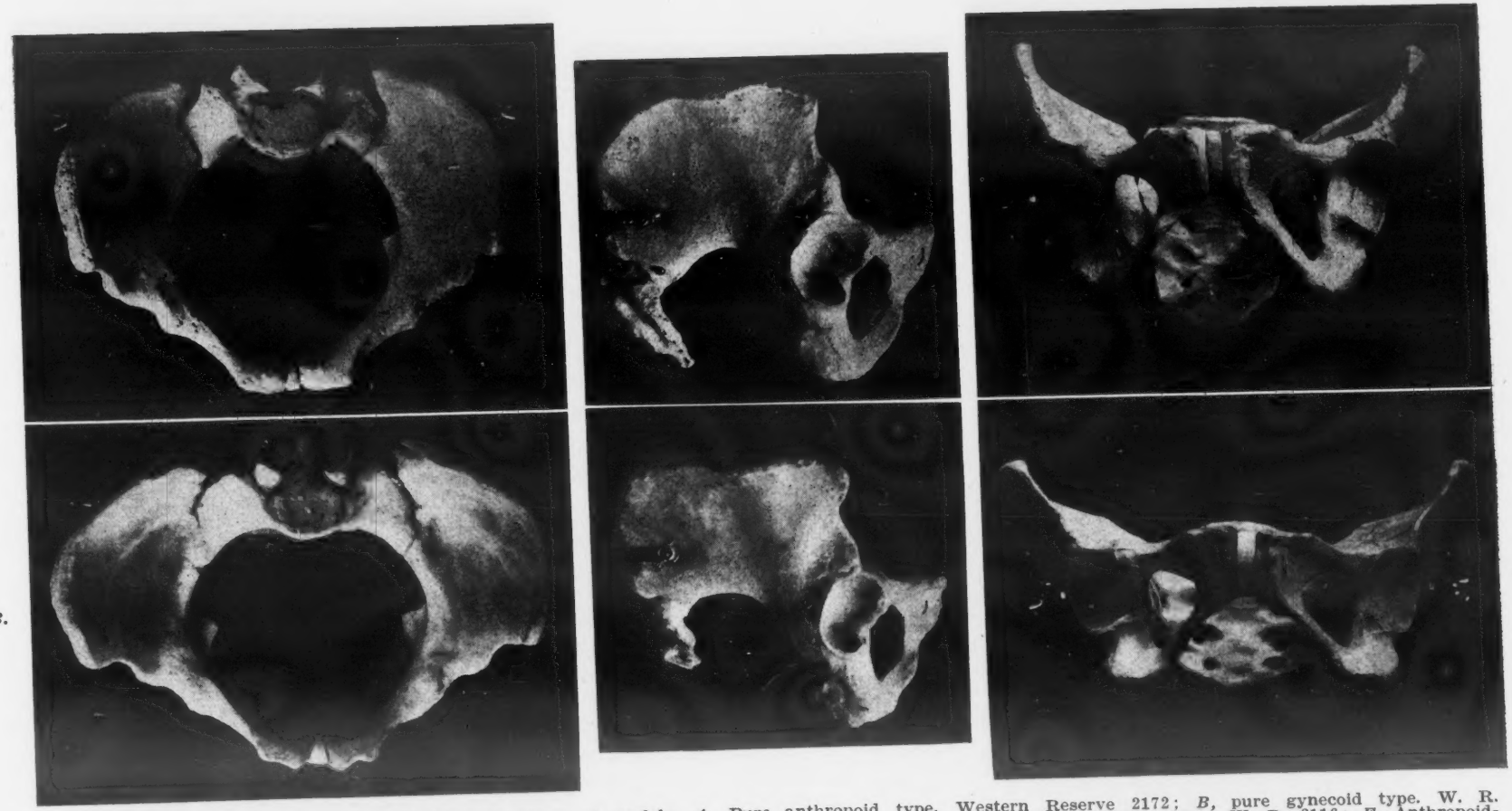
Gynecoid Type.—Fig. 7B (Prototype Fig. 3B). Western Reserve No. 2337, White.

In skeletal material, as well as in roentgenologic examinations, excellent examples of all types are seen. When it comes to the problem of selecting one good example of the type, minor deviations from the classic prototype are prone to exist. The specimen selected to reveal the characteristic gynecoid features is a fairly representative specimen. The shape of the inlet is quite characteristic. The ischial spines, however, are slightly more prominent than occurs in the classical gynecoid. This specimen was selected because the inlet, sacrosciatic notch and subpubic arch conform to the classical gynecoid prototype.

The Gynecoid-Flat (Mixed) Type.—Fig. 7I (Prototype Fig. 3I). Western Reserve No. 415, White.

This type in general appearance is quite similar to the flat-gynecoid type Fig. 7N. The chief difference between these types is shown in the

(Text description, continued on p. 168.)



Figs. 7*A-P.*—Inlet, lateral and subpubic arch views of models. *A*, Pure anthropoid type. Western Reserve 2172; *B*, pure gynecoid type. W. R. 2337; *C*, pure android type. W. R. 1256; *D*, pure platypelloid type. W. R. 1208; *E*, anthropoid-gynecoid (mixed) type. W. R. 2116; *F*, Anthropoid-android (mixed) type. W. R. 3210; *G*, gynecoid-anthropoid (mixed) type. W. R. 715; *H*, gynecoid-android (mixed) type. W. R. 2476. *I*, Gynecoid-flat (mixed) type. W. R. 415; *J*, android-anthropoid (mixed) type. W. R. 2708; *K*, android-gynecoid (mixed) type. W. R. 603; *L*, android-flat (mixed) type. W. R. 454; *M*, flat-android (mixed) type. W. R. 1924; *N*, flat-gynecoid (mixed) type. W. R. 2860; *O*, male pelvis. Department of Anatomy, College of Physicians and Surgeons; *P*, asymmetrical pelvis. W. R. 111.

of Physicians and Surgeons; *P*, asymmetrical pelvis. W. R. 1[illegible]

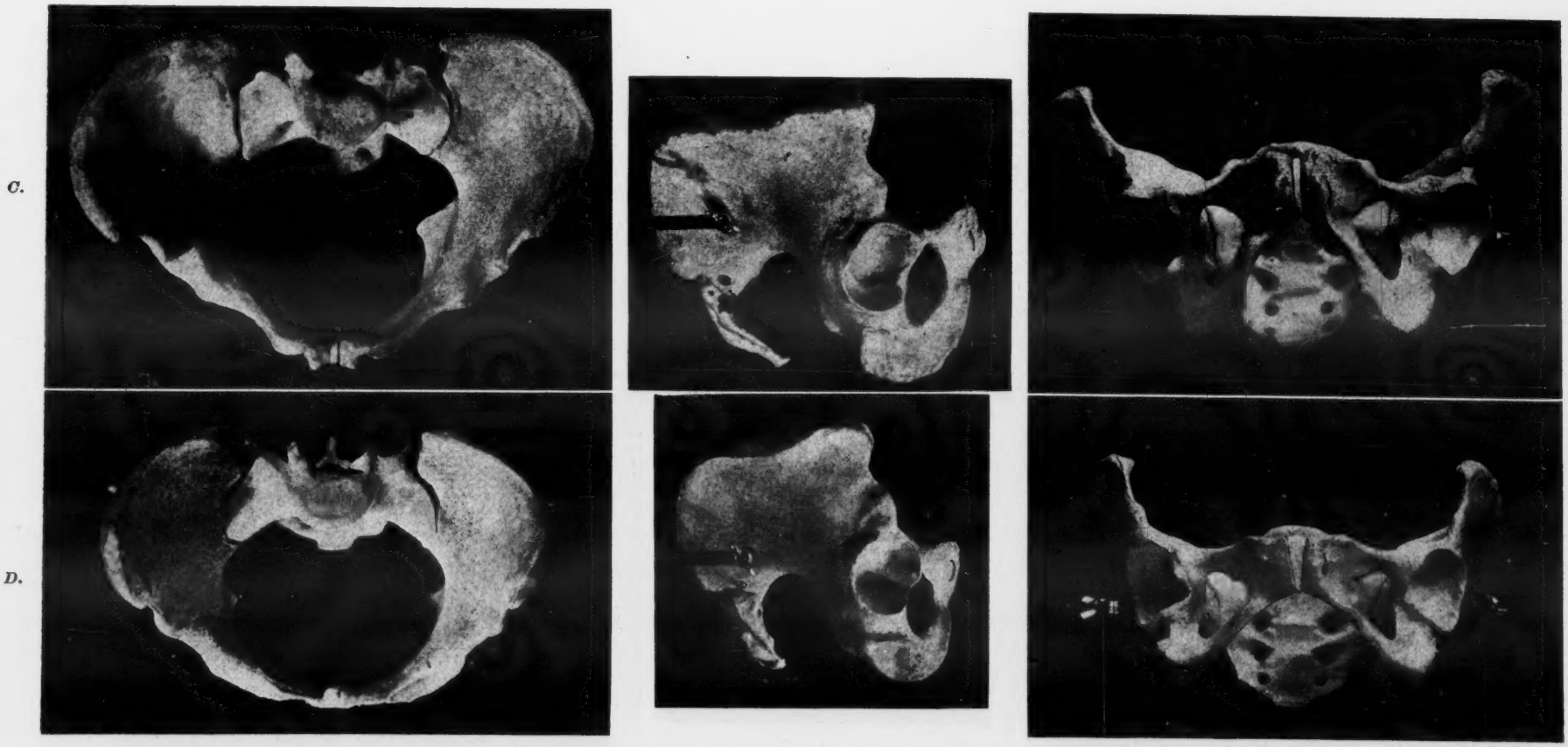


Fig. 7.—*C*, Pure android type, W. R. 1256; *D*, pure platypelloid type, W. R. 1208.

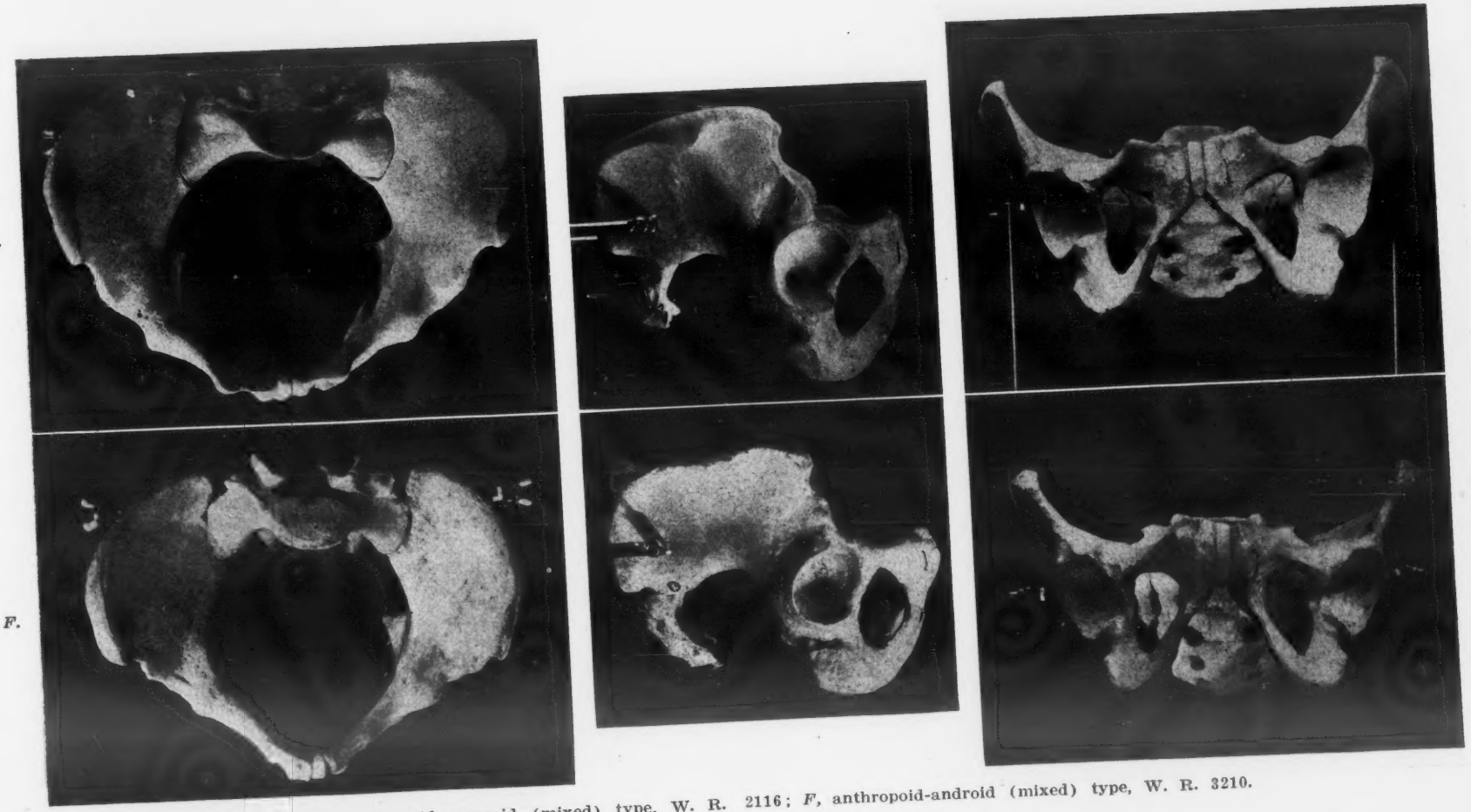


Fig. 7.—*E*, Anthropoid-gynecoid (mixed) type, W. R. 2116; *F*, anthropoid-android (mixed) type, W. R. 3210.

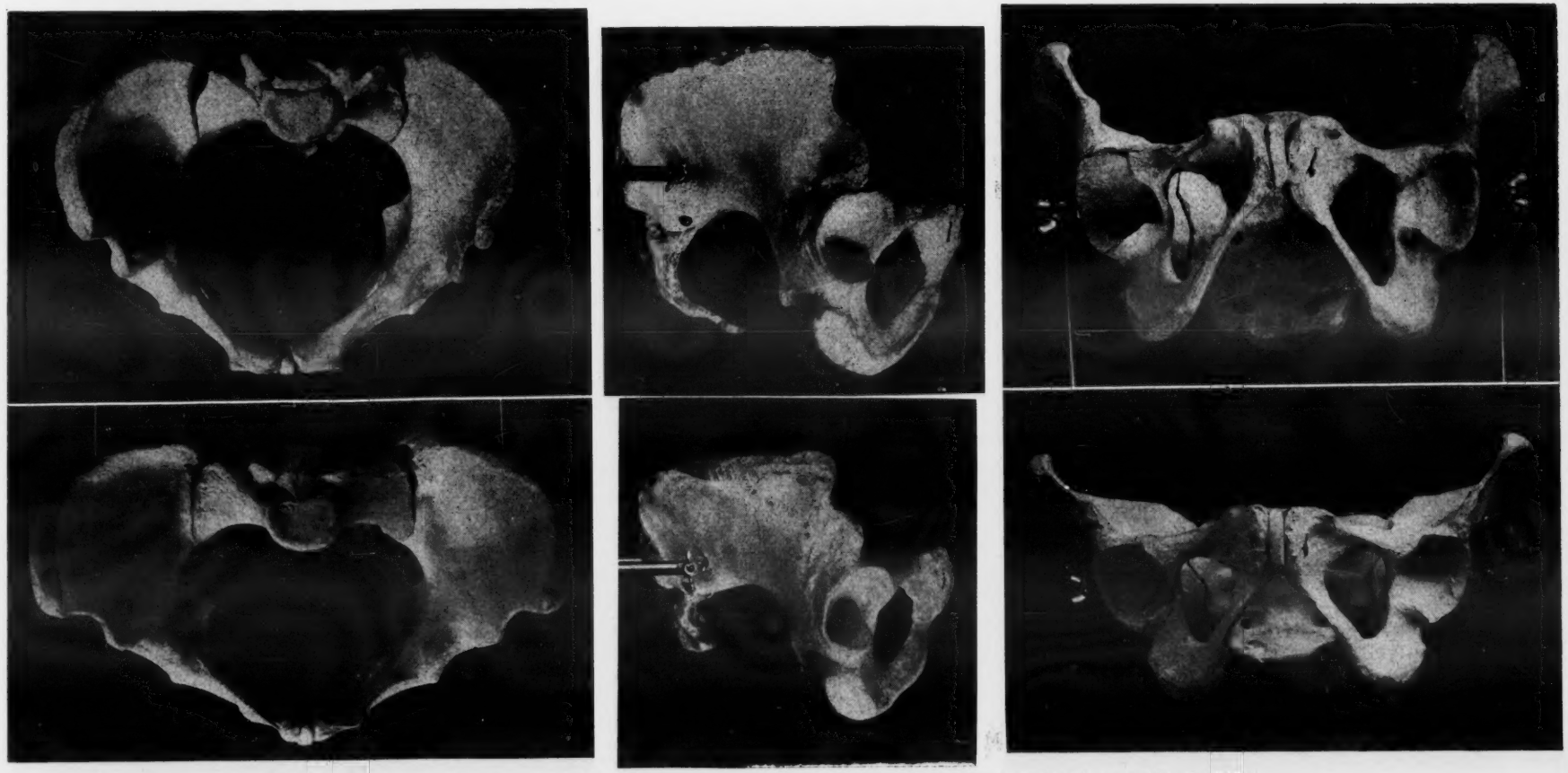


Fig. 7.—*G*, Gynecoid-anthropoid (mixed) type, W. R. 715; *H*, gynecoid-android (mixed) type, W. R. 2476.

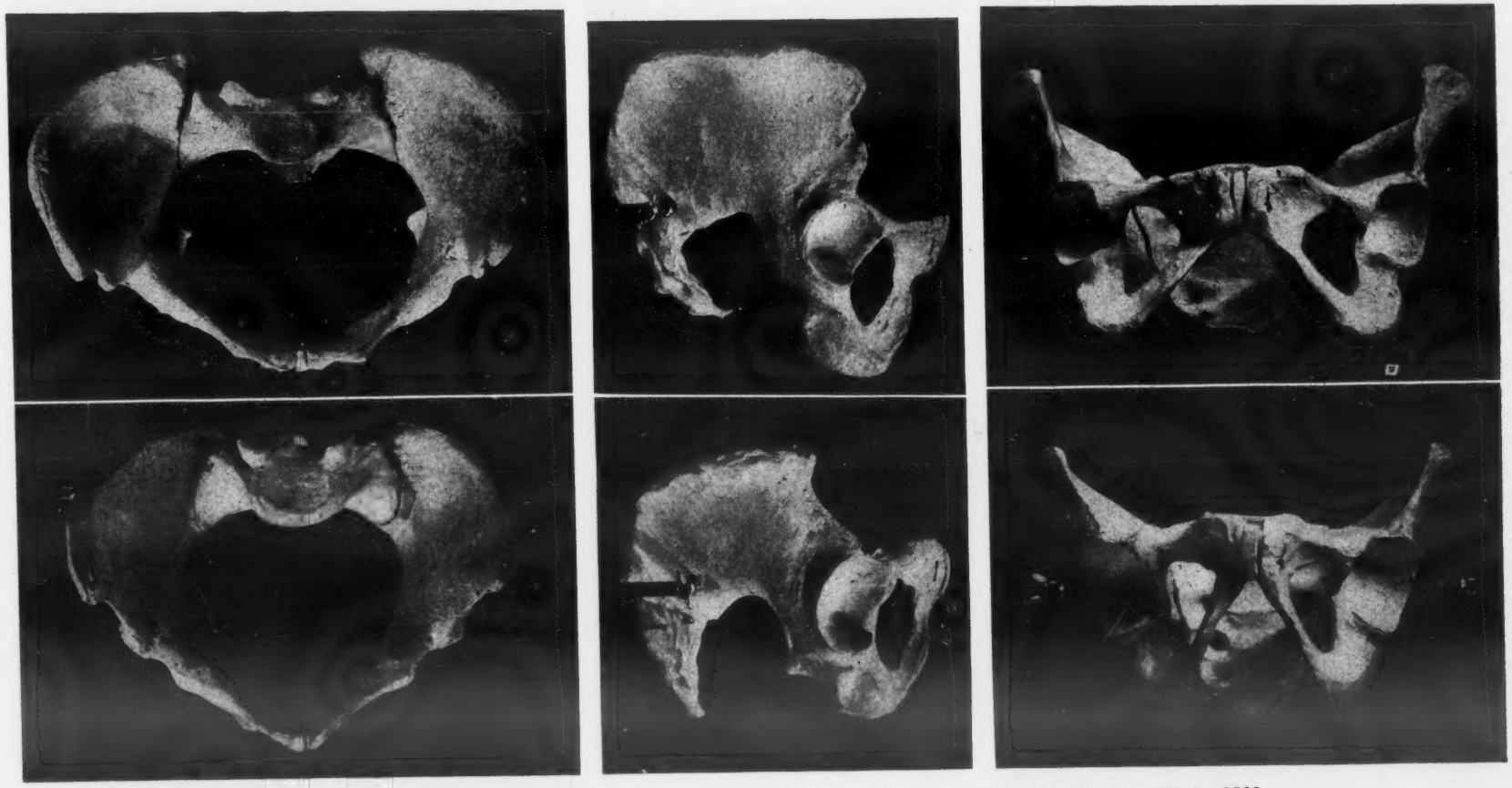


Fig. 7.—*I*, Gynecoid-flat (mixed) type, W. R. 415; *J*, android-anthropoid (mixed) type, W. R. 2708.

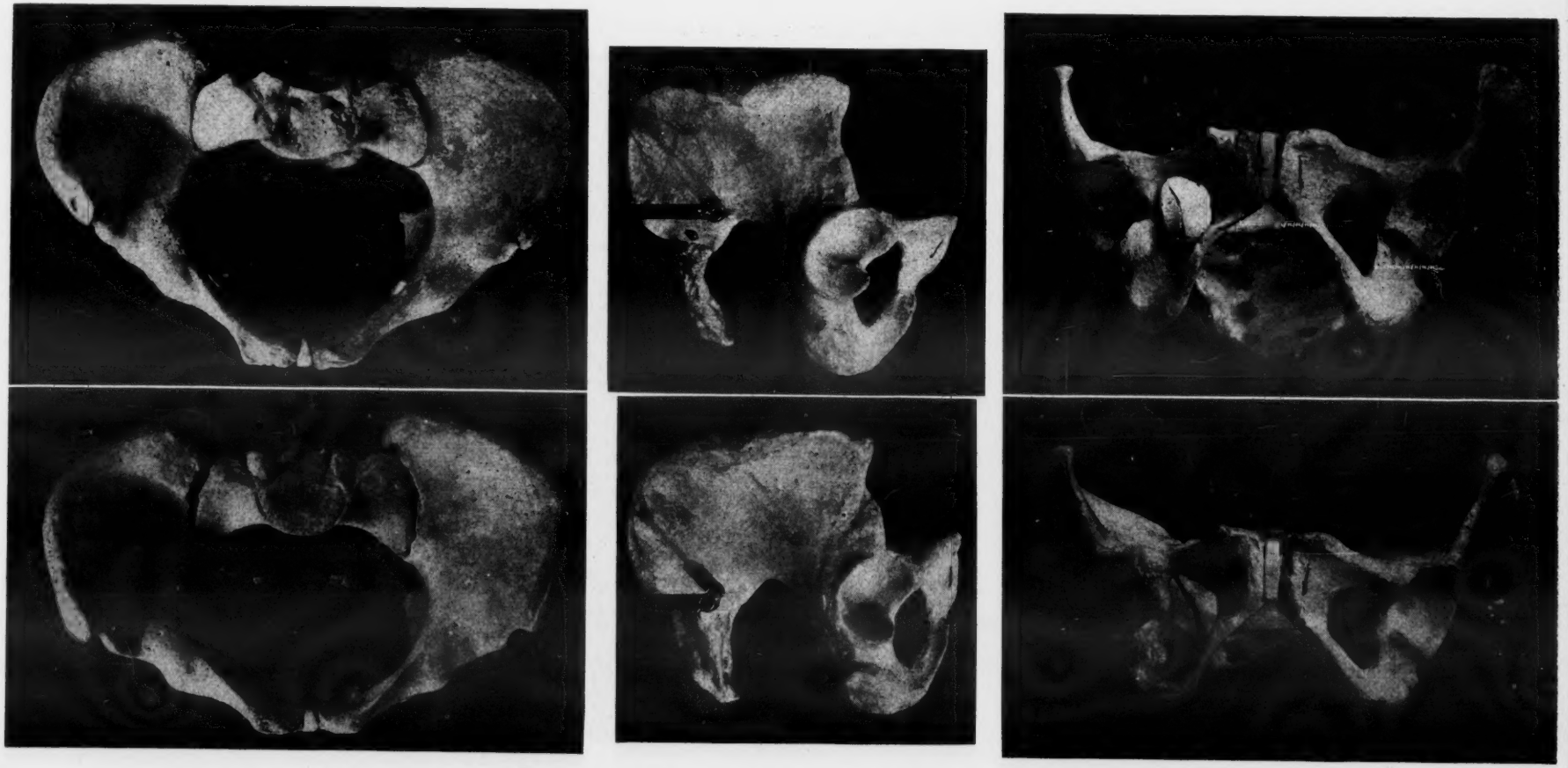


Fig. 7.—*K*, Android-gynecoid (mixed) type, W. R. 603; *L*, android-flat (mixed) type, W. R. 454.

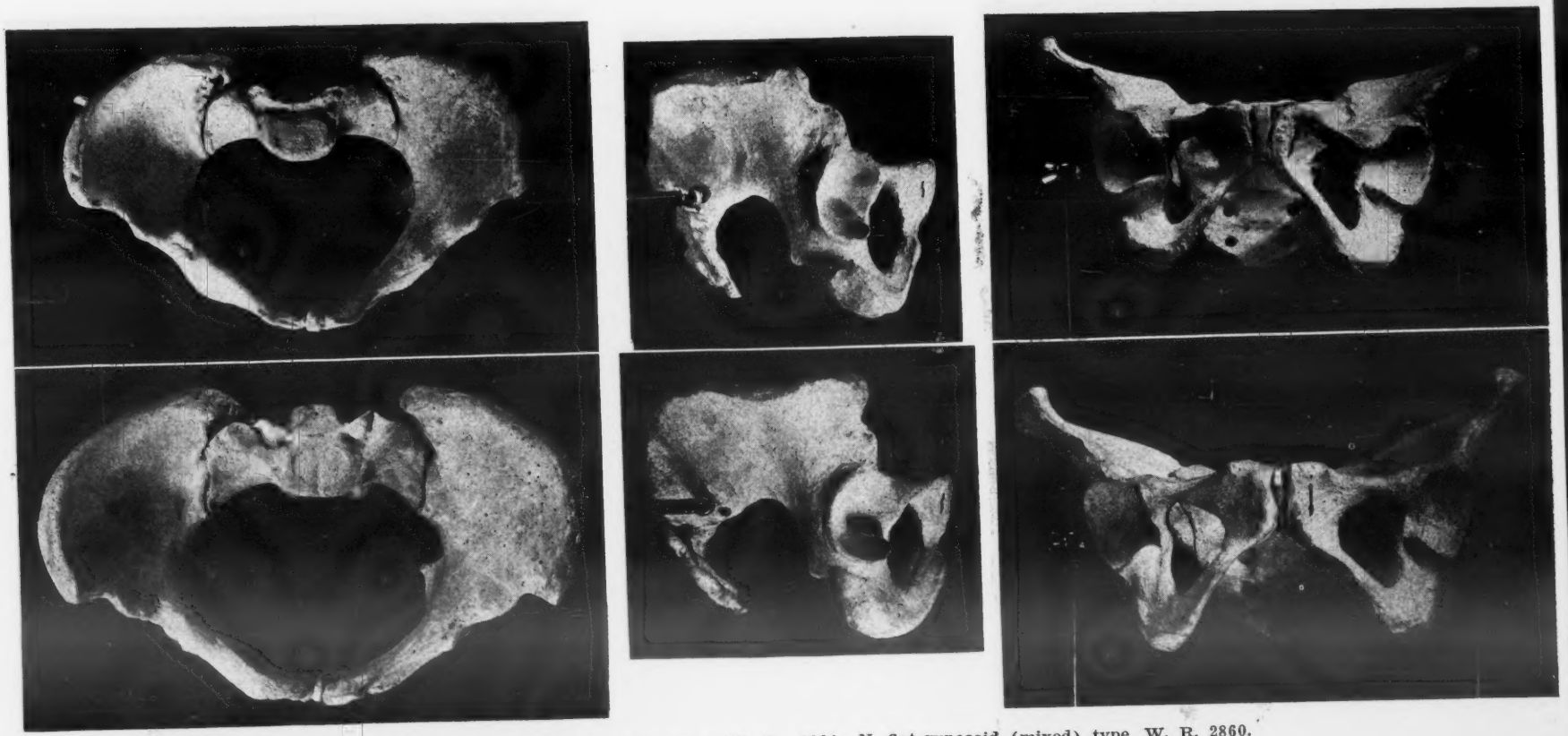


Fig. 7.—*M*, Flat-android (mixed) type, W. R. 1924; *N*, flat-gynecoid (mixed) type, W. R. 2860.

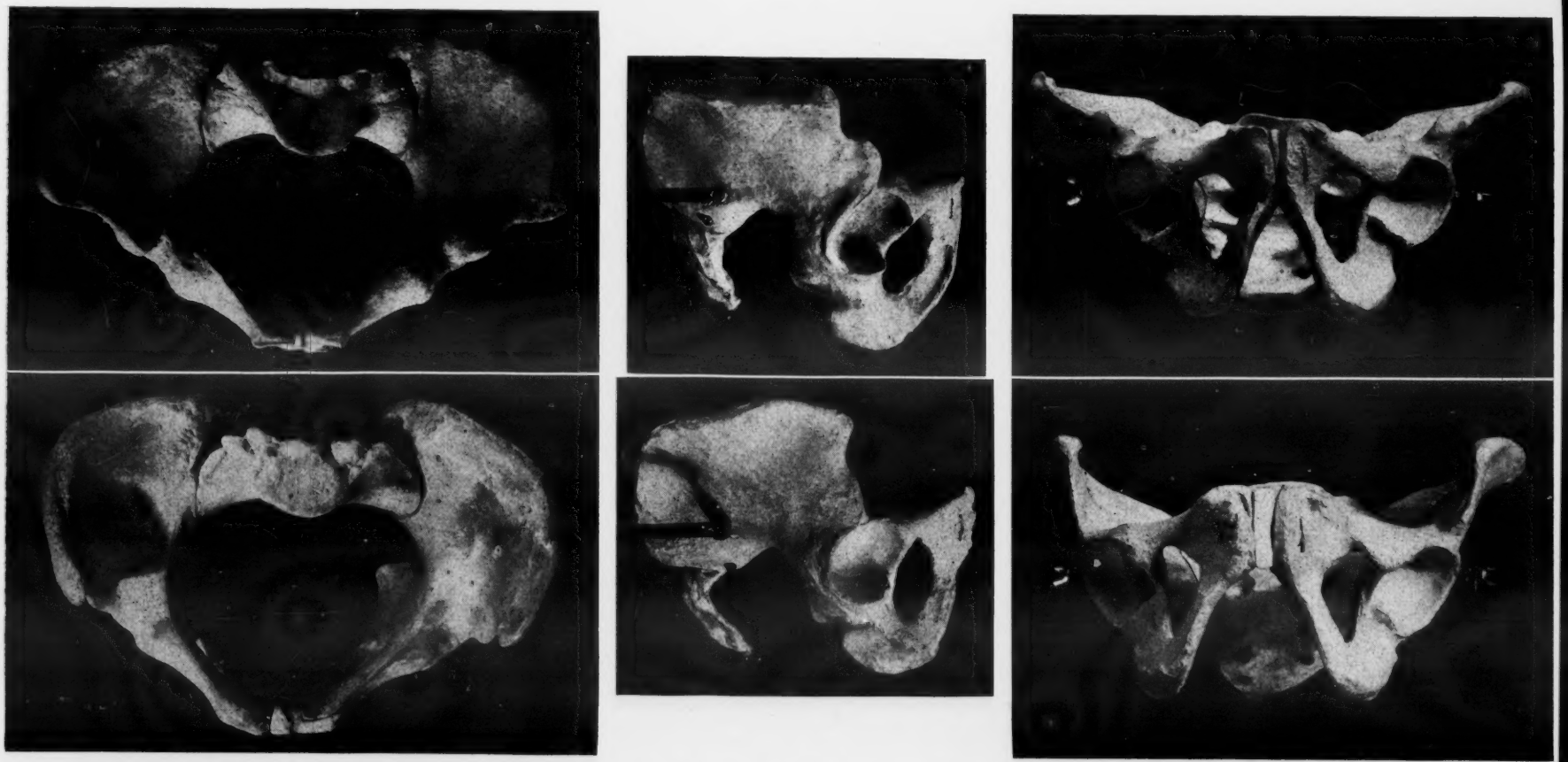


Fig. 7.—*O*, Male pelvis. Department of Anatomy, College of Physicians and Surgeons; *P*, asymmetrical pelvis, W. R. 111.

position of the widest transverse diameter. In the gynecoid-flat type, the widest transverse diameter is placed forward on the anteroposterior diameter, the sacrosciatic notch is wide and the section of ilium over the apex of the notch, between the origin of the widest transverse diameter and the sacroiliac synchondrosis is ample. The sacrum has a marked concavity with a forward sacral tip and six segments.

Flat-Gynecoid Type (Mixed).—Fig. 7N (Prototype Fig. 3N). Western Reserve No. 2860, White.

This type has a more flattened appearance than the gynecoid-flat. The posterior segment is flat because the widest transverse diameter is closer to the sacrum. This feature causes a narrower sacrosciatic notch.

True Platypelloid Type (Pure).—Fig. 7D (Prototype Fig. 3D). Western Reserve No. 1208, Negro.

This example shows the characteristic features of a pure flat type. The inlet, a transverse flat oval is well formed and the widest transverse diameter tends to favor the midcoronal axis of the pelvis. The specimen is a small example of the classical type.

True Android Type (Pure).—Fig. 7C (Prototype Fig. 3C). Western Reserve No. 1256, White.

The prototype calls for a wedge-shaped inlet caused by a flat posterior segment and a narrow forepelvis with straight iliopectineal lines radiating from the symphysis. At lower levels the side walls converge to a narrow subpubic arch, and the lateral view shows a narrow, masculine sacrosciatic notch with a forward sacrum. The example selected does not reveal all these classical features. It will be noted that the posterior segment is not so characteristically masculine as the prototype demands, and the inlet has an elongated appearance. This particular example was selected because it shows the marked side-wall convergence and a narrow subpubic arch which represent typical masculine characters. The lower sacrum has a forward inclination. It is the transverse sacral concavity which detracts from the typical masculine appearance of the posterior segment at the inlet in this particular example.

Android-Gynecoid Type (Mixed).—Fig. 7K (Prototype Fig. 3K). Western Reserve No. 603, White.

This is an unusually fine example. The posterior segment is very masculine in appearance. The sacrosciatic notch is narrow. The anterior segment is well formed and gynecoid in appearance. The combined segments give a slightly flat effect. The sacrum has six segments and is straight with an average to backward inclination.

Gynecoid-Android Type (Mixed).—Fig. 7H (Prototype Fig. 3H). Western Reserve No. 2476, Negro.

This is a gynecoid or normal pelvis with a narrow anterior segment. Upon casual study of the posterior segment, it might be supposed that the segment is not characteristically gynecoid. It appears to present a flat shape. This fact is due in part to the presence of an overhanging sacral promontory associated with a backward inclination to the sacrum. The specimen was selected to show this particular type of sacral variation. However, if the shape of the posterior segment is viewed at the plane of the inlet, where the iliopectineal lines, if continued, would cross the anterior surface of the first sacral segment, the gynecoid characters of the posterior segment will be evident. The masculine character of the forepelvis expressed by a narrow angle behind the symphysis is also present.

Android-Anthropoid Type (Mixed).—Fig. 7J (Prototype Fig. 3J). Western Reserve No. 2708.

The prototype calls for a flat posterior segment and a long narrow anterior segment, thereby producing an elongated anthropoid appearance (Fig. 3J). The specimen selected demonstrates these features satisfactorily. More characteristic examples have been recognized especially in roentgenograms of living women. The posterior segment in the illustrated example is not quite as flat or masculine in appearance as in the prototype. However, this particular specimen shows an excellent example of a straight sacrum and the inlet appearance is made characteristic by a narrow anterior segment associated with convergence of the side walls at lower levels.

Flat Android Type (Mixed).—Fig. 7M (Prototype Fig. 3M). Western Reserve No. 1924, Negro.

This is an excellent example. Although the angle of the anterior segment is wide, the iliopectineal lines are straight and this feature, in conjunction with the flat posterior segment, gives a flat wedge-shaped angular appearance to the pelvic inlet. This particular specimen is a small example of the prototype, and it is doubtful if it would be adequate for delivery of a child of average size. Certain examples of this type show convergence of the side walls at a lower level.

Android Flat Type (Mixed).—Fig. 7L (Prototype Fig. 3L). Western Reserve No. 454, White.

This type is difficult to distinguish from the flat-gynecoid type. The widest transverse is close to the promontory and the iliopectineal lines curve acutely inward toward the sacroiliac synchondrosis over the apex of the sacrosciatic notch. As a result, the posterior segment has a flatter posterior segment than occurs in the flat gynecoid. The anterior segment is wider and the anterior sagittal diameter is usually shorter than in the flat gynecoid type. The straight sacrum has a slightly backward inclination.

Typical Masculine Pelvis.—Fig. 70, College of Physicians and Surgeons, Dept. of Anatomy.

This fine example of a male pelvis needs no comment. It was selected to show all the characteristic male features which have been described, i.e., heavy bones, narrow Gothic subpubic arch, male symphysis, converging side walls, narrow sacrosciatic notch and a characteristic wedge-shaped inlet.

Common Asymmetrical Type.—Fig. 7P, Western Reserve No. 111, White.

This example was included in the teaching series for general anatomic interest. Slight asymmetry is common in occurrence. In a series of 215 complete roentgenologic examinations in living women, pelvic asymmetry was observed in 4 per cent of the cases.

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HERPES GESTATIONIS*

With a Report of Two Cases and a Survey of the Literature

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HERPES gestationis is an uncommon cutaneous complication of pregnancy, being a chronic polymorphous exanthema characterized by recurrent crops of grouped bullae and vesicles on erythematous bases and associated with severe pruritus.

Ormsby and Montgomery[34] definite herpes gestationis as being a variety of dermatitis herpetiformis, differing from that disease only in its exciting cause—pregnancy. Accordingly, one may expect in this syndrome a considerable degree of variability as to the time of onset, signs, symptoms, and response to therapy.

First described by Bunel[31] in 1811, the condition has been variously referred to as dermatitis multiformis gestationis, herpes circinatus bullosus, hydroa gravidarum, hydroa herpetiformis, pemphigus pruriginosus, and prurigo gestationis. The generally accepted term "herpes gestationis" was first suggested by Milton[1] in 1872.

Comprehensive summaries of the literature have been previously recorded by Duhring,[2] Tommasi,[6] and Howard.[13]

Although its incidence is not very great, the disease is probably more common than one would be led to believe from the number of cases reported in the obstetric literature. Irving[19] has stated that no patients with this dermatosis had been admitted to the Boston Lying-in Hospital in a recent 20-year period. Turner and Zakon[30] through personal communications found that many obstetricians had never encountered the disease. In a review of the American literature for the past 10 years, we have been able to collect references to 15 cases of herpes gestationis and mention of 18 others. To this group, we add two additional cases, making a total of 35 cases in all.

Etiology

The etiology of the disease is unknown. Many authors feel that the cutaneous lesions result from injury to the vasomotor nerves by toxins or ferments manufactured by the fetal tissues or by cells of the chorionic epithelium. These substances may ordinarily be neutralized by antiferments or as seems more plausible, are formed only in quantity when the chorionic villi disintegrate. Inasmuch as placentas of even normal women witih no demonstrable organic disease are prone to show areas of

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infarction, dissolution of tissue at the time of such accidents may well explain the periodic exacerbations of the disease.[13]

Several investigators have advanced the theory that renal insufficiency accounts for the appearance of the disease. Perrin[3] found urea, total nitrogen, and chloride retention. Presumably, there would be an accompanying failure to eliminate toxins or similar bodies of high molecular weight.

Sayer[26] felt that the disease represents a toxic disturbance induced by impaired hepatic function. In his opinion, the liver is unable to cope with the added burden of fetal metabolism and fails to function in its usual role of detoxification. Del Vivo[10] also noted hypofunction of the liver as determined by laboratory examinations in a case which he observed. Sechi[12] found a normal liver function test on his patient.

Del Vivo, however, advocated the theory that the disease represents an anaphylactic mechanism resulting from sensibilization to certain antigens as yet unknown, and which may differ from time to time. His patient presented a cutaneous hypersensitivity to globulins and albumins from her own placenta. Sulzberger and Rostenberg[17] pointed out that the nature of the presumptive allergens is, as yet, unknown, and routine cutaneous testing is therefore impossible. Werther[7] likewise expressed the belief that the cutaneous manifestations in herpes gestationis were an allergic phenomenon. Crosti's patient showed no cutaneous allergic reactivity to follicular, lutein, or placental preparations, but injections of these substances were capable of causing significant reacutizations of the objective and subjective symptoms.[11]

A few investigators have considered an endocrine disturbance to be a factor of prime importance in the etiology. Tommasi[6] suggested that the disease resulted from ovarian hypofunction. Sechi[12] in 1932 employed corpus luteum hormone in the treatment of a case of herpes gestationis and noted immediate regression of the eruption. An acute exacerbation immediately post partum was likewise controlled. He concluded, therefore, that herpes gestationis was due to a disturbance in the production of corpus luteum hormone. Gilman[15] in 1933 reported similar success. Kampf[27] in 1940 noted that corpus luteum extracts seemed to lessen the pruritus of the disease and to cause the eruption to slowly regress.

Rostenberg[28] noted, in his patient, that the gonadotropin was protracted for several months after parturition. Weidman[21] observed that the degree of pruritus varied with fluctuations in the gonadotropic principle, there being a greater quantity in those with mild pruritus and a lesser in those with severe pruritus.

Elliott[20] in 1938 reported a case of skin rash occurring in association with choriocarcinoma secondary to a hydatidiform mole. Inasmuch as the cutaneous manifestations appeared about the time the chorioma appeared to grow, and inasmuch as they became more extensive with increased activity of this malignant growth, he concluded that the skin rash should be classified as herpes gestationis. He suggested that the Aschheim-Zondek test might be positive in high dilutions in cases of herpes gestationis during pregnancy, and that this titer might remain high even post partum when an acute exacerbation of the disease was noted following delivery. The Aschheim-Zondek test is said to be usually negative by the seventh post-partum day. A Friedman modification of the Aschheim-Zondek test was performed on one of our patients

on the tenth post-partum day, and this was negative despite a severe exacerbation of her dermatitis at that time.

Antoine[9] ascribed the disease to a toxicosis produced by the ovum in association with an unknown virus.

In many cases reported in the literature, herpes gestationis occurred only in pregnancies terminating in the birth of infants of the same sex.[23] Lewis[22] reported a case in which the woman developed herpes gestationis during two previous pregnancies, and each time the offspring proved to be a male. On a third occasion she delivered a female, and no symptoms of the disease were noted throughout her pregnancy. On a fourth pregnancy, however, the disease again appeared; and as was prognosticated, a male was later delivered. This hypothesis was refuted by Costello in 1941, when he reported two successive pregnancies in the same patient, severely complicated by herpes gestationis, the first time a boy being delivered, the second time a girl.

Signs and Symptoms

Although the disease may appear at any time during pregnancy, it is more common to the latter half of gestation. It rarely appears before the fourth month of pregnancy. The disease seems to be more frequent in primiparous and uniparous patients. The greatest number of cases have been reported in the age group of 30 to 35 years. The disease may recur with monotonous regularity in each of many successive gestations, or return intermittently every second or third pregnancy.[13]

The onset of the disease is marked by a severe generalized burning sensation succeeded by a pruritus. Then a patchy erythema develops on the extremities, occasionally on the trunk. During the next 24 hours, these erythematous patches enlarge and herpetiform crops of small vesicles appear. In some areas, the vesicles are noted to surround a red macule or a slightly raised and edematous plaque, either at its junction with normal skin or aligned on a palpably elevated margin. The vesicles soon coalesce to form tense, thick-walled bullae of assorted sizes. A few of the bullae subsequently appear to arise from apparently normal skin. Upon rupture of the bullae, the serous crusts eventually fall away, leaving as a rule only a brownish pigmentation. Mucosal lesions are rare but do occur.

The pruritus associated with the disease is intense and persistent; and in the early stages is disproportionately in excess of the amount of the eruption. Excoriations of the skin are not prominent, however, even though the patient generally indulges in considerable scratching. This is due to the fact that the lesions do not readily rupture, and that they tend to refill immediately after being evacuated.

Once the disease appears, it usually progresses to the termination of gestation, showing many cyclic flare-ups and remissions. The exacerbations are usually accompanied by mild to severe constitutional symptoms of albuminuria, dyspnea, dyspepsia, fever, malaise, and neuralgic pains. Eosinophilia during the acute exacerbation may range as high as 50 per cent. During the first few days post partum, a final acute exacerba-

tion is usually followed by a permanent regression of all signs within two weeks to three months. Occasionally, following delivery, episodes of severe pruritus and burning precede the onset of the first few menstrual periods. Infrequently, a bullous or vesicular eruption may appear. Such flare-ups are termed herpes menstrualis recidivans.

Differential Diagnosis

The diagnosis of herpes gestationis must be differentiated at times from other toxic dermatoses such as drug eruptions, erythema multiforme bullosum, impetigo herpetiformis, and pemphigus. The latter two are usually fatal. In many cases, the diagnosis will be contested, even amongst dermatologists, pending final outcome of the illness.

Prognosis

The prognosis for the mother is fairly good, although a few cases with fatal outcome have been reported. The prognosis seems worse, the earlier in pregnancy the disease appears. The disease is likely to occur earlier and to be of increasing severity in succeeding pregnancies.[24]

The prognosis for the child is much less hopeful. The incidence of spontaneous abortions, monstrosities and stillbirths is high among women afflicted with herpes gestationis or predisposed to it. Costello[23] reported his case in which the woman delivered a normal child with her first pregnancy, and an anencephalic infant with spina bifida with the second. Isbister[8] reported a case in which the first born, a 6¼-pound infant died on the fourth day after delivery without obvious reasons. In the second pregnancy, the same patient delivered a stillborn infant. In del Vivo's case, a second pregnancy terminated in the delivery of a premature infant with bilateral microphthalmus and a cleft palate.

Nevertheless, a number of normal infants have been obtained at term. Infants delivered of mothers afflicted with herpes gestationis must be guarded against intercurrent infections during the first year of life.

Cutaneous lesions may occur in the child, but this apparently has little to do with the prognosis. Tommasi[6] reported two cases in which lesions of the skin developed on the infants after birth, but disappeared within a few days, leaving no evidence of their former presence. Milton[1] reported a case presenting an alternation of stillbirths and live babies, demonstrating cutaneous lesions in both the healthy and dead children. Furthermore, one from the group of dead children showed no evidence whatever of an abnormality of the skin.

Therapy

The treatment for herpes gestationis is not too efficacious, and the course of the disease in the majority of cases seems little influenced by the therapy. The prevention of secondary infection and general supportive measures are the most important. Locally, aqueous astringent

baths, abscission of the larger bullae, and topical applications of antiseptic lotions are advised. Irradiation of local lesions sometimes affords relief.

Heiman[29] suggested the intravenous injection of 10 c.c. of a 10 per cent solution of strontium bromide to afford relief from the generalized pruritus.

Fowler's solution has been suggested as therapy, and in some cases has been highly effective. It is best given in full therapeutic dosage, and still better if administered in intermittent courses.

Eichmann[4] reported one case in which cure was obtained by daily 300 c.c. infusions of Ringer's solution, intended to change the mineralization and ion concentration of the blood.

In some cases, autohemotherapy, serum from normal pregnant women especially if of the same stage of gestation, or injections of horse serum have been effective. Ormsby reported excellent results in one case, administering 20 c.c. intramuscularly at 5-day intervals of the blood serum obtained from another normally pregnant female. On the other hand, Brittman[5] had only partial success with human serum, but reported a permanent cure by the intramuscular injection of boiled milk.

Tommasi[6] reported two cases in which ovarian extract was administered with eventual success. Turner and Zakon[30] gave their patient 600,000 units of progynon B and 70 milligrams of proluton over a one-week period with no noticeable effect. The success of Gilman, Kampf, and Sechi has been previously noted.

Sulfa drugs have been tried in a few cases. Turner and Zakon used sulfanilamide, 40 grains per day for 11 days, with no noticeable or subjective improvement. Sulfapyridine used subsequently gave similar results. On the other hand, Lewis[33] maintained a patient on one gram of sulfathiazole daily for the last month of her pregnancy with successful amelioration of all her subjective complaints. He advised further use of chemotherapy in the treatment of herpes gestationis, and admonished that once relief was obtained by the drug, prompt relapse of the disease would follow unless a maintenance dose were continued.

Fortunately, it is seldom necessary to induce premature labor in these cases, though it is the only method which will permanently allay symptoms in the majority of cases.

Gellhorn[14] performed a cesarean section in a 34-year-old multipara who had gone three weeks past term, and showed no signs of impending labor despite four attempts at medical induction. Herpes gestationis had developed only two weeks before, and was rapidly becoming more severe. At operation, the patient was delivered of a normal 10½-pound infant. The mother died 4 days post partum of peritonitis and sepsis. The infection was thought to be due to the fact that the incision had to be made through diseased skin with its pus-filled vesicles which could not be sufficiently sterilized though particular precaution had been taken. No vaginal examination was performed at any time prior to operation. Carter and Pearse[18] reported a similar case in which peritonitis developed 4 days postoperatively from a cesarean section for cephalopelvic disproportion, from which the patient successfully recovered.

Mayr,[25] in discussing the literature and reporting six cases of this disease, concluded that the only treatment for the severe cases of herpes gestationis is interruption of the pregnancy, and admonished that the physician should not hesitate to undertake this procedure.

Likewise, Adair and Stieglitz[16] advise interruption of the pregnancy in all cases where therapeutic measures not contraindicated by the pregnancy have been tried and failed, and where the expectant woman's life or health are endangered, or the itching is so intense as to disturb the tranquillity necessary for an otherwise physiologic state to reach its normal end.

Two cases are herewith presented, with reference to the type of treatment and results obtained in each case.

Case Reports

CASE 1.—This patient was a 27-year-old white housewife, who was transferred to Kings County Hospital on November 25, 1942. Two weeks before, in another institution, she had been delivered at term of a 5 pound, 4 ounce living female infant. Shortly after delivery, she developed a generalized bullous and vesicular skin eruption which was severely pruritic. This had persisted despite treatment in the other institution, and was characterized by recurrent crops of vesicles and bullae.

Her pregnancy had been uneventful except for the appearance of urticarial-like macular and iris skin lesions on the hands and thighs in the fifth month of this pregnancy. These lesions had burned and itched severely. The patient noted several remissions and exacerbations of the rash; and only two weeks before delivery, she had a short-lived flare-up during which bullae and vesicles had appeared.

Past history was negative. This was her second pregnancy. The first had terminated spontaneously at 2½ months' gestation in November, 1941.

At the time of transfer to us, general physical examination was essentially negative except for the skin eruption. Few areas of clear skin remained. The bases of the various bullae consisted of erythematous halos. Some vesicles and bullae appeared to arise from normal skin. The larger bullae measured 1.5 centimeters in diameter at their bases. All of the bullae were under tension but did not rupture spontaneously. Some of the bullae had a purulent content. Several lesions were noted on the mucous membranes of the mouth.

Laboratory determinations were as follows: W.B.C. 12,000 with 81 polymorphonuclear leucocytes and 19 lymphocytes per 100 cells; hemoglobin determination 62 per cent. Blood Wassermann was negative. The blood urea was 22 mg. per 100 c.c. of blood; creatinine 1.17; and sugar 80. The sodium chloride determination was 485 mg. per 100 c.c. of blood. Urinalysis was negative.

A biopsy of one of the skin lesions was obtained. This was reported by the pathologists (Dr. W. W. Hala and Dr. Joseph Rini) as follows: "Section is one of skin in which continuity of the epidermal lining is disrupted by a ruptured bullous lesion, the cavity of which is filled with erythrocytes and serum. The epidermis shows hypertrophy with elongations and tree-like branching of the rete cones. Some intra- and intercellular edema is noted. There is moderate edema of the papillary bodies, with marked dilatation and congestion of the capillaries and

vascular channels, many of them containing perivascular infiltrations of eosinophiles and neutrophiles, some lymphocytes. Considerable endothelial proliferative activity is also present. Numerous eosinophiles and neutrophiles are present in the upper cutis."

The diagnosis clinically and pathologically was herpes gestationis.

Treatment was by abscission of the bullae, local applications, and daily permanganate baths. One blood transfusion was given for supportive measures. Sulfathiazole medication was tried on several occasions, but the patient always noted an increase in the intensity of the pruritus during the time of administration and the skin eruption likewise became more marked. The pruritus of the eruption could be alleviated temporarily by adrenalin hypodermically or by ephedrine sulfate orally.

The disease continued to be characterized by recurrent crops of vesicles and bullae, but each exacerbation was less severe than the previous one. On January 3, 1943, the patient was discharged from the hospital. At this time the skin was almost completely cleared up and the vital signs were normal. There have been no recurrences.

CASE 2.—The patient was a 19-year-old white Italian housewife who entered Kings County Hospital for the first time on November 19, 1940, because of a severe skin eruption associated with pregnancy. Eight days before admission, she had noted a small bleb below the umbilicus. During the next several days, a severely pruritic rash developed over the entire abdomen; and just before admission to the hospital, new lesions had developed on the arms, breasts, back, and thighs. Her last menstrual period had begun on April 21, 1940; and the expected date of confinement had been set as January 28, 1941. This was her first pregnancy. She had been receiving adequate prenatal care.

There was no previous history of skin diseases or allergic reactions. There had been no previous operations or serious illnesses except for influenza two years before.

Physical examination was essentially negative except for a generalized skin eruption, presenting erythematous urticarial-like lesions, varying in diameter from ½ to 1½ centimeters. Many of the lesions had small vesicular centers, confluent in several areas, notably over the entire abdomen, with small vesicles and bullae. Pelvic measurements were ample. The fundus of the uterus extended 3 fingers above the umbilicus. Fetal heart tones were good.

Laboratory data: R.B.C. 4,450,000 with 75 per cent hemoglobin. W.B.C. 28,450 with 56 per cent polymorphonuclear leucocytes, 16 per cent lymphocytes, and 28 per cent eosinophiles. Blood Wassermann was negative. Urinalysis was negative. Blood urea was 24 mg. per 100 c.c. of blood; creatinine 1.15; sugar 80.

A diagnosis of herpes gestationis was made clinically.

The course was characterized by severe remissions and exacerbations of the skin eruption. She complained of joint pains on several occasions. Treatment consisted of local applications of permanganate solution, abscission of the bullae, and by mouth both calcium gluconate and ephedrine sulfate.

On December 5, 1940, she went into labor spontaneously and after 10 hours, delivered without incident a premature 4 pound, 15 ounce male infant. The child was weak and lethargic, and lived only 24 hours.

Subsequent to delivery, there was no acute flare-up of the eruption. A few new crops of bullae and vesicles appeared from time to time, but the pruritus gradually became less. When discharged on December 30, 1940, her general condition was good and the skin lesions had almost completely disappeared, leaving areas of brownish pigmentation.

The patient was readmitted on July 17, 1942, at which time she was hospitalized for one week because of a spontaneous abortion of eight weeks' gestation. There were no skin lesions associated with this pregnancy. Postabortal course was uneventful.

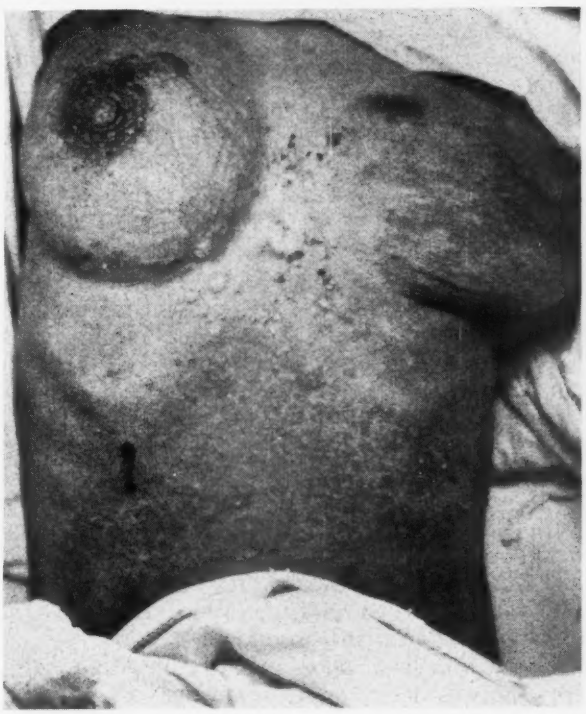

Fig. 1.—Case 2. Seven days post partum. Note the large vesicles grouped together beneath the right breast.

The patient again entered Kings County Hospital on March 3, 1943. Six days before admission, the patient noted blebs over both feet associated with a severe pruritus. The lesions rapidly spread up the legs, and on admission had already appeared on the breasts and abdomen. She complained of a severe generalized burning and pruritus. Her last menstrual period had begun on November 15, 1942. Expected date of confinement had been placed on August 22, 1943.

Physical examination was again essentially negative except for the generalized skin eruption, consisting of erythematous plaques, bullae, and vesicles. Pelvic examination confirmed the diagnosis of an intrauterine pregnancy of approximately 4 months' gestation.

A diagnosis of herpes gestationis was again made, and treatment was begun. Despite permanganate baths and topical applications of antiseptic lotions following abscission of the larger vesicles and bullae, the eruption and general condition of the patient became rapidly worse and a therapeutic abortion was considered. A remission then developed, and

conservative measures of treatment were continued with the hopes of maintaining the pregnancy until term.

Twice weekly for several weeks, injections intramuscularly of serum obtained from pregnant women of approximately the same gestational period were given. After each injection, the patient complained of a severely intense pruritus, and many new crops of lesions appeared. Autohemotherapy was likewise tried and similar results were obtained. Histamine, in the form of torantil tablets, units 20, were given twice daily for eight weeks with no essential relief. Sulfathiazole was resorted to on several of the exacerbations with no relief objectively or subjectively.

Supportive measures such as small repeated blood transfusions, liver extract intramuscularly, high vitamin and high caloric diet, etc., maintained the patient in fairly good general condition despite repeated exacerbations and remissions of the skin eruption. As the pregnancy progressed, the patient's mental status became more depressed and melancholic. At times, she complained of severe pruritus and burning. Occasionally, hot flashes were also noted objectively.

On May 16, the patient developed regular rhythmical uterine contractions which were very painful to her. The cervix seemed partially effaced on rectal examination, and the presenting part seemed to dip into the pelvis. Premature labor seemed impending, but several small repeated doses of morphine gave complete relief and the pregnancy continued normally thereafter. A similar episode was noted approximately one month later, on June 21.

Early in July, the patient developed an abscess in the right buttock following an intramuscular injection. An incision and drainage was performed, with the evacuation of 12 ounces of greenish purulent material. Culture of this revealed *Streptococcus hemolyticus* and *Staphylococcus aureus hemolyticus*. One week later, she developed a similar abscess in the suprascapular area which also had to be incised and drained. Both lesions healed rapidly following incision and drainage. Sulfanilamide was placed in both wounds.

The patient went into labor spontaneously on August 18, 1943. After a 9-hour labor, she was delivered spontaneously of a living 4 pound, 14 ounce healthy female infant.

Although the patient had had almost a complete remission of her skin eruption for two weeks prior to delivery, an acute exacerbation occurred almost immediately post partum. Numerous new skin lesions developed, and these were associated with an intense pruritus and burning. The patient was given massive doses of stilbestrol therapy without subjective or objective improvement. After two weeks, the eruption gradually subsided, the mental outlook improved, and only occasional new lesions appeared. She was discharged on September 18, 1943, at which time the general condition was good and the skin almost completely cleared.

The infant was discharged with the mother, and has remained in good health subsequently. It is interesting to note that the infant, though free of any lesions at delivery, developed a mild erythematous and maculopapular eruption on the face, chest and abdomen 6 hours later. This disappeared spontaneously on the third day of life.

Numerous laboratory tests were perfomed on the patient both before and after delivery. Urinalysis was negative throughout her course except for an occasional trace, or one-plus albuminuria. The white

blood cell counts varied between 9,000 and 18,000. There were a minimal number of eosinophiles noted on differential examination. The red blood cell count varied between 3.5 and 4.5 million cells per c.c. The sedimentation rate was 24 mm. in 45 minutes. Rh-factor was positive. (The father was also determined to be Rh-positive.) Prothrombin time was determined to be 80 per cent of normal. Blood urea ranged between 21 to 25 mg. per 100 c.c. of blood; sugar 76 to 78 mg. Prenatally, the albumin was found to be 3.5 with the globulin 2.9, a total protein value of 6.4. Cholesterol esters were 118, with free cholesterol 72. Total cholesterol determination was 190. Calcium was 9.9; phosphorus 3.4; and phosphatase 1.9 units. The van den Bergh was direct negative. Icterus index was 4.0. An x-ray examination of the chest revealed no old or recent pulmonary or pleural pathology. An electrocardiogram was normal.

Post partum, at the height of an acute exacerbation of the disease, a cephalin flocculation test was done to determine liver function, and this was reported as normal. On the tenth post-partum day, a Friedman test was performed and this likewise was reported as negative.

On October 7, 1943, the patient developed a severe generalized burning sensation with the reappearance of many new vesicles and bullae. She presented herself for readmission on October 10. Shortly after admission to the hospital, she began to menstruate for the first time post partum. This period lasted three days. With the subsidence of her menstrual flow, the lesions also began to disappear. The patient was discharged on October 17, at which time almost all the lesions had again disappeared. Diagnosis on discharge was herpes menstrualis recidivans. Several succeeding periods were likewise accompanied by the appearance of an eruption associated with pruritus, but each time the course was less severe and soon subsided. Her general condition is good at present.

Summary

1. Two cases of herpes gestationis with reference to their treatment and results obtained therefrom, have been presented. The previous literature has been reviewed.

2. Herpes gestationis is a polymorphous exanthema differentiated from similar forms because of its etiology rather than its morphologic characteristics.

3. The disease is characterized by its chronicity, with remissions and exacerbations throughout the course of gestation; and by a tendency to recur in subsequent pregnancies with increasing severity.

4. The disease responds poorly, if at all, to any form of therapy.

5. The prognosis for the mother is good; it is less so for the offspring. Many cases can be carried to full term in spite of the disease.

The authors are indebted to Doctor E. A. Gauvain and Staff of the dermatological service at Kings County Hospital for the privilege of presenting the dermatological aspects of these cases.

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ORAL SUBSTITUTION THERAPY WITH ETHINYL ESTRADIOL AND ALPHA-ESTRADIOL

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WITHIN recent years a new phase in ovarian substitution therapy—the oral phase—has been developed. With injection therapy previously favored by the availability of potent hypodermic preparations, a return to the oral method of treatment has been initiated by the discovery and manufacture of active, orally effective estrogenic substances such as diethylstilbestrol, ethinyl estradiol and conjugated estrogens equine.

The Endocrine Department of this clinic was founded in 1930, and since that time several thousand women have been treated with estrogens for ovarian deficiency. Following this background of unpublished material, data have been kept and published on 502 patients treated orally and hypodermically with estrone, estradiol benzoate and diethylstilbestrol dipropionate.[1] An additional report has been made on 138 patients treated orally with conjugated estrogens equine.[2] In the present study, the clinical response of 47 patients to ethinyl estradiol has been tabulated along with previously unpublished observations on 80 patients treated with oral alpha-estradiol (dihydroxyestrin). It has thus been possible to compare the relative clinical effectiveness of six estrogenic substances which have been employed in the treatment of 767 patients.

Ethinyl Estradiol

Reports appearing in the literature on ethinyl estradiol appear to be quite favorable.[8, 9, 12-16] This estrogen was prepared in 1938 by Inhoffen and Hohlweg[17, 18] by replacement of the hydrogen of the seventeenth carbon atom in estradiol with an ethinyl group. In our studies, enteric coated ethinyl estradiol tablets* of 0.01 mg., 0.02 mg., 0.05 mg., and 0.1 mg. were used. Uncoated tablets of 0.05 mg. were also employed.

A total of 47 patients ranging in age from 24 to 60 years were treated with ethinyl estradiol. Included in this series were 17 cases of natural menopause, 15 cases of artificial menopause and 15 other cases, part of which were associated with hypoestrinism. Results in this series are summarized in Table I.

Analysis of Results With Ethinyl Estradiol

When ethinyl estradiol was given, it was possible to duplicate any therapeutic effect obtained with diethylstilbestrol dipropionate. Furthermore, equally effective results were obtained with smaller amounts of material. Indeed, it was observed that a dose as low as 0.02 mg. of ethinyl estradiol produced a definite therapeutic response. While

*The ethinyl estradiol tablets (Estinyl) used in this investigation were supplied through the courtesy of Dr. Max Gilbert and Dr. William R. Bond of the Schering Corporation, Bloomfield, N. J.

TABLE I. RESULTS WITH ETHINYL ESTRADIOL*

PATIENT	AGE	REMARKS (A)	HOT FLASHES	NERVOUSNESS	MENSTRUATION (B)	SPECIAL TYPE (C)	DAILY DOSE IN MG.	REACTIONS (D)	UTERINE BLEEDING (E)	VAGINAL SMEARS (F) BEFORE	VAGINAL SMEARS (F) AFTER	% RELIEF OBTAINED
NATURAL MENOPAUSE												
1. Mrs. K. B.	51		++	++	O		0.05	0		4		100
							0.1	0				100
2. Mrs. N. K.	47	M	+++	++++	O		0.1	0	B	2	1	100
							0.05	0				100
3. Mrs. L. L.	48	M; IN; P; A	+++	+++	O		0.1	0		4	4	50
							0.2	0				100
4. Mrs. E. T.	50	H; IN; M	++++	+++	O		0.06	0				75
5. Mrs. M. R.	51	Worried	++++	++++	O		0.1	0				50
							0.2	0				75
6. Miss F. M.	42	A; P	++++	++++	O		0.05	0				50
							0.1	0				100
7. Mrs. A. T.	46		++++	+++	O		0.05	0	B	2	1	25
							0.1	0				100
							0.2	0				100
8. Miss M. W.	41	IN	++	+++	I		0.05	0				100
							0.1	0				100
9. Mrs. M. W.	56	IN	++++	++	O		0.05	0				?
							0.1	0				50
10. Mrs. E. R.	49	H	++++	+	O		0.2	0				100
11. Miss L. B.	45	A; M	+++	++	R		0.01	0				0
							0.02	0				25
							0.05	0				50
							0.1	0				100
12. Mrs. F. B.	51		++++	+++	O		0.05	0	B	1		50
							0.1	0				85
							0.2	0				100
13. Mrs. B. O.	48	A; H	++	+	I		0.02	0		1		50
							0.05	0				100
							0.1	0				100
14. Mrs. R. L.	40	Menstruates only part of one day; M	++	+++			0.01	0		3	3	0
							0.02	0				10
							0.05	0				50
15. Mrs. A. R.	56		+	+	O		0.1	0		2		100*
16. Mrs. I. D.	50		+	+	O		0.01	0				50
							0.02	?				100
17. Mrs. N. D.	60	IN; M	++++	+++	O		0.05	0				75
ARTIFICIAL MENOPAUSE												
18. Miss E. M.	56	A; M; H	++	++	O	U	0.01	0		1		0
							0.02	0				25
							0.05	0				50
							0.1	0				100
19. Mrs. C. O.	33	A; P; H	++++	++++	O	2—O	0.1	0		4	3	100*
20. Mrs. O. P.	52	A	++++	+++	I	X	0.02	0				25
							0.05	0				75
							0.1	0				100
21. Mrs. P. A.	42	A	++++	++++	O	U	0.1	?		1		50
						1½—O	0.3	0				85
22. Miss A. M.	52	A	++++	++	O	U	0.1	0				50
						2—O	0.2	N, D				85
23. Mrs. R. B.	44	A; H	+	++	O	U	0.1	0		2		50
						2—O	0.2	0				65
24. Mrs. S. C.	53	A; G	++	+++	O	X	0.1	0	B			85
25. Mrs. R. S.	38	F; M	+	++++	O	U	0.1	?		2		50*
						1—O						
26. Mrs. S. S.	45		++++	+++	O	2—O	0.05	0				100
							0.1	0				100

*See Key to Table I, page 184.

TABLE I—CONT'D

PATIENT	AGE	REMARKS (A)	HOT FLASHES	NERVOUSNESS	MENSTRUATION (B)	SPECIAL TYPE (C)	DAILY DOSE IN MG.	REACTIONS (D)	UTERINE BLEEDING (E)	VAGINAL SMEARS (F)		% RELIEF OBTAINED
										BEFORE	AFTER	
ARTIFICIAL MENOPAUSE												
27. Mrs. F. M.	47	H; husky voice; emotional	++++	+++	O	2—O	0.01	0	B	3	1	0
							0.02	0				35
							0.04	0				75
							0.05	0				100
28. Mrs. G. W.	38	C; M; H	+	++++	O	$1\frac{3}{4}$—O	0.1	V				100
						X	0.01	0				20
29. Mrs. J. M.	35	A; H	++	++	O	U	0.2	N		4		100*
						$1\frac{3}{4}$—O	0.05	N				75
30. Mrs. H. M.	46	A	+++	++	O	U	0.05	0				50
						1—O	0.1	0				100
31. Mrs. C. M.	38	M	++++	+	O	2—O U	0.1	N		2	1	100
32. Mrs. H. W.	31	A; IN; M	++++	+++	O	2—O	0.05	0				50
						U	0.1	0				90
OTHER CASES												
33. Miss F. C.	44	A; H; treatment given for therapeutic test	0	+++	O	U	0.1	0		1		0
34. Mrs. M. R.	36	A; H; SA; (G)	0	+	O		0.1	0		2		35
35. Mrs. A. M.	29	M; S; marital trouble	+	++++	R	1—O	0.05	0	L	1		25
							0.1	0				35*
36. Mrs. E. O.	31	A; F	0	++	R		0.1	0	L	2		50*
37. Mrs. E. W.	29	A; H; P; SA	+	++++	I		0.05	0				0
							0.1	0				25*
38. Miss H. A.	24	SA	0	0	O		0.1	N V				
39. Mrs. A. H.	25	A; DM; F; trochanteric obesity	0	++	I		0.05	0				50
							0.1	0				50*
40. Miss I. R.	36		+	++	R		0.1	0	L	4	1	100
41. Mrs. P. S.	36	Eunuchoid; infantile uterus; menstruation began age 17; F; S	+	+	R		0.05	T	B	2		100*
42. Mrs. M. S.	37	Manic depressive psychosis; treatment given for therapeutic test	0	++++	I	$1\frac{3}{4}$—O	0.1	0		2		0
43. Mrs. F. D.	37	A; F; M; C	0	++++	R		0.05	0	L	2	1	50*
44. Mrs. M. M.	53	Psychoneurosis; treatment given for therapeutic test	?	++++	O		0.01	0		3		0
							0.02	0				0
							0.1	?				0*
45. Mrs. M. K.	29	Hypopituitary; secondary hypoovarian; ht. 57 in.; primary amenorrhea and asthenia	0	+	O		0.05	N T				0
46. Mrs. M. P.	34	Headaches at menstruation	0	+	R		0.1	0		4	3*	50
47. Mrs. J. R.	47	A; C; M	0	+++	R		0.03	0		2		25
							0.1	?				0

some patients required as much as 0.2 mg., optimal dosage for most patients averaged 0.05 mg. to 0.1 mg. The average per cent of improvement on ethinyl estradiol at various dosage levels is tabulated below:

DOSE IN MG.		0.01	0.02	0.05	0.1	0.2
Natural menopause	Improvement	17%	46%	64%	86%	95%
Artificial menopause	Improvement	7%	28%	71%	83%	83%
Other hypo-ovarian	Improvement			37%	31%	

Mental depression in the menopause proved most refractory to therapy. However, ethinyl estradiol was much more beneficial than any of the other natural estrogens used. In this respect, its action was similar to that afforded by diethylstilbestrol dipropionate.

Vaginal smears were normal in 6 of 27 patients examined before treatment, while the remaining 21 patients showed varying degrees of estrogen deficiency. Ten of these patients had vaginal smears taken after treatment and improvement was noted in eight cases. Excessive discharge and infections of the vagina and cervix frequently prevented the use of this test for assay.

Undesirable Effects With Ethinyl Estradiol

Menstrual bleeding was caused by ethinyl estradiol in five patients who were no longer menstruating because of artificial or natural menopause. Menstruation was delayed in four patients who always menstruated regularly and it was very profuse in another patient.

True toxic reactions to ethinyl estradiol were observed in seven patients with the following symptoms: nausea—five; vomiting—two; dizziness—one; nervousness—one; and "generally worse and more tense"—one. Patient 22 had nausea and dizziness on 0.2 mg. but not with 0.1 mg. Patient 28 had vomiting on 0.1 mg. but not on 0.01 mg. Patient 29 had nausea on 0.2 mg. but on 0.05 mg. this became markedly

KEY TO TABLE I

(a) A—Asthenia; C—Difficulty thinking and concentrating; DM—Dsymenorrhea; F—Frigidity; G—Globus; H—Headache; IN—Insomnia; M—Mental depression; P—Palpitation; S—Sterility; SA—Secondary amenorrhea.
(b) I—Irregular; 0—No longer menstruating; R—Regular.
(c) O—Ovaries removed; U—Uterus removed; X—X-ray menopause.
(d) D—Dizziness; N—Nausea; T—"Nervous tension;" V—Vomiting.
(e) B—Some type of uterine bleeding or menstruation caused by the tablets; L—Tablets caused menstruation to be late.
(f) I—Normal; 2—Slight deficiency of estrogen; 3—Moderate deficiency; 4—Severe deficiency.
(g) Pituitary tumor; Hirsuitism; Hormone assay of urine: 19 C.U. of androgens per 24 hours.

*Remarks after treatment: Patient 15 had a constant pain at the end of the urethra which was not relieved; Patient 19 had had a nervous breakdown from which she did not recover; Patient 25 had improvement in hot flashes and breast soreness only; Patient 29 had migraine headaches from which she obtained no relief; Patient 35 had a marked increase in the size of her breasts; Patient 36 had an increase in her libido associated with a lessening in asthenia and nervousness; Patient 37 had an increase in libido and in the size of her breasts; Patient 39 had less asthenia and nervousness, but she was not otherwise benefited; Patient 41 had relief of the hot flashes, but the menstruation, which was scanty before treatment, became more profuse and painful; Patient 43 had fifty per cent improvement of symptoms, but the effect was at least partly pharmacodynamic; Patient 44 had an increase in the "sweats" on 0.1 mg., proving that they were not hot flashes. Breast soreness developed showing effectiveness of material; Patient 46 had abnormal vaginal smears because of marked vaginitis.

reduced. While no attempt was made to use smaller dosage with the other cases, it was evident that the above three patients improved when the dose was decreased and it is believed that most patients would tolerate small amounts of the drug.

Toxicity for the entire group, covering all dosage levels, was 14 per cent, but the incidence was very much less with doses under 0.05 mg. daily.

There were five questionable reactions on ethinyl estradiol. With patient 16 insomnia developed while 0.02 mg. was being taken but later disappeared although the tablets were continued. Dizziness began in patient 21 with 0.1 mg. but cleared up when 0.3 mg. was taken. Patient 25 developed a "gnawing in the stomach" on 0.1 mg. but this symptom was noticed occasionally before taking the tablets. Patient 44 began to "sweat" more with 0.1 mg. but not with smaller doses. Patient 47 had a poor appetite on 0.1 mg. but tolerated 0.03 mg.

There was an increase in fullness and tenderness in the breasts in many cases treated with ethinyl estradiol, and three patients complained of severe soreness. Several mentioned that the nipples and areola darkened in color; while others, in whom breast soreness was present before treatment reported improvement while taking the tablets. Several patients noted an increase in vaginal moisture or leucorrhea during treatment. This has also been observed when other potent estrogens are employed, either orally or parenterally.

Eleven of the patients who had no reactions with enteric coated tablets of ethinyl estradiol were given 0.05 mg. uncoated tablets. None of these patients had a reaction, and symptoms were relieved as effectively with the uncoated tablets as with the enteric coated tablets.

Alpha-Estradiol

The uncoated tablets of alpha-estradiol* (dihydroxyestrin) a natural estrogenic substance found in the ovary and blood of human beings, were standardized by weight to contain 0.1 mg., 0.2 mg. and 0.5 mg. They were taken from one to three times daily depending on the dose prescribed. Alpha-estradiol was also obtained as a stable, chemically pure, crystalline substance. It was highly insoluble in water, but some of it was dissolved in sesame seed oil with the use of a solvent. This oil, containing various amounts of alpha-estradiol, was taken by patients in 20 drop doses, three times daily.

The following doses represent the largest amount of alpha-estradiol given to each patient per day.

DAILY DOSE OF ALPHA-ESTRADIOL	NUMBER OF PATIENTS	DAILY DOSE OF ALPHA-ESTRADIOL	NUMBER OF PATIENTS
0.2 mg.	5	0.8 mg.	2
0.3 mg.	2	1.0 mg.	10
0.4 mg.	17	1.5 mg.	9
0.5 mg.	27	2.0 mg.	1
0.6 mg.	6	3.0 mg.	1

Results With Alpha-Estradiol

While a favorable response was obtained with alpha-estradiol administered orally as tablets, improvement was definitely less in degree. Only patients with milder symptoms who did not wish to take injections were given alpha-estradiol. Sedatives were not used in any of the cases.

*These tablets, called Progynon-DH, were obtained from the Schering Corporation, Bloomfield, N. J.

Alpha-estradiol, orally, did not relieve hot flashes very well in doses less than 0.5 mg. daily, and a better response was obtained with 1.5 mg. daily. This natural estrogen had a good tonic effect and increased the sense of well-being in patients.

Results regarding migraine, dysmenorrhea, premenstrual tension, etc., are not included since these conditions were frequently not associated with hypoestrinism, and improvement in each case was predicated on the response to estrogens of patients with hypoestrinism. However, where these conditions were associated with the syndrome, they were frequently relieved by estrogen therapy. In some instances it was felt that the pharmacodynamic or drug action of the estrogen was responsible for relief. This has been noted frequently in previous observations with diethylstilbestrol dipropionate.

Toxicity With Alpha-Estradiol (Oral)

In general, untoward reactions to alpha-estradiol were negligible. While taking alpha-estradiol, 1 mg. daily, one patient began to flow early, one late and one had severe dysmenorrhea. Only one patient developed nausea and vomiting, a reaction caused by many other types of medication. There was no true toxicity. One patient felt nervous and more tense. Hyperestrinemia might have existed previously in this patient since the breasts had been sore and firm for two years. Unfortunately, a hormone assay of the urine was not made in this case. Two other patients receiving alpha-estradiol complained of breast soreness. Hormone assays of some of the other patients treated in this series have been reported previously.[4]

Comparison With Other Oral Estrogens

After this study, it is possible to evaluate the strength of six estrogenic substances used at the clinic. The data on estrone, estradiol benzoate, diethylstilbestrol dipropionate[1] and conjugated estrogens-equine[2] were obtained from previous observations. Their relative strengths, judged on a weight basis milligram per milligram, are listed in Table II. Other desirable and undesirable results are also estimated as to degree of importance.

It was impossible to obtain a strong estrogenic effect with estrone, estradiol benzoate or alpha-estradiol with the amount of material given, such as was produced by conjugated estrogens, diethylstilbestrol dipropionate or ethinyl estradiol. Of course, the hypodermic administration of estrone and estradiol benzoate gave a strong estrogenic response, the latter being stronger than the former, but the comparison in Table II was limited to material absorbed from the gastrointestinal tract. One milligram of conjugated estrogens-equine was roughly equivalent to 0.3 mg. to 0.5 mg. of diethylstilbestrol dipropionate or 0.05 mg. to 0.1 mg. of ethinyl estradiol. Since the strong effect of 0.05 mg. to 0.1 mg. of ethinyl estradiol was not produced by alpha-estradiol[6-11] in the doses used, 1 mg. to 1.5 mg., it was known that ethinyl estradiol was at least 15 to 30 times more effective than alpha-estradiol. While Hohlweg and Inhoffen[17] reported that ethinyl estradiol was 15 to 20 times as effective as alpha-estradiol, Soule[8, 9] stated that it was 50 to 70 times as effective. Thus, in adding the ethinyl radical to alpha-estradiol, a potent estrogen effect has been obtained with greater economy.

TABLE II. EFFECT OF ESTROGENS GIVEN

1 MG. OF EACH	ESTRONE	ESTRADIOL BENZOATE	ALPHA-ESTRADIOL	CONJUGATED ESTROGENS	DIETHYLSTILBESTROL DIPROPIONATE	ETHINYL ESTRADIOL
Quantitative	Very little	Some	More	Strong	Stronger	Strongest
Qualitative	Good	Good	Good	Good	Not as good	Good
Uterine bleeding	0	?	?	+	++	+++
Development of breasts	0	Slight	Slight	Good	Stronger	Strongest
Relief of mental depression	0	?	+	+++	++++	+++++
Relief of hot flashes	Very little	Some	More	Strong	Stronger	Strongest
Toxicity per optimum effective dose	0	0	0	0	+	+

Discussion

The oral method has several obvious advantages over the hypodermic. It is cheaper, timesaving and more convenient to the patients and doctor. It avoids local reactions frequently obtained with hypodermic injections.[5] It allows frequent administration of material which has proved to be advantageous, as pellet implantation of hormone[3] is more effective than intermittent doses by injection.

The oral method also has some disadvantages. Patients are inclined to treat themselves, while the hypodermic method permits constant management by the physician. The stronger preparations have a toxic effect on some patients. This toxicity is of a very mild nature and diminishes when the dosage is cut. In some patients a small dose was well tolerated whereas a larger amount caused symptoms of toxicity. Gastrointestinal symptoms are believed to be central, possibly medullary, rather than local in origin. Enteric coating of the tablets did not prevent the symptoms. Patients who tolerated enteric coated tablets also tolerated noncoated tablets. Prior to this study, patients who had had a toxic reaction to diethylstilbestrol dipropionate administered orally were given injections, but the nausea and vomiting still persisted. The toxic manifestations cleared up rapidly when medication was discontinued, leaving no permanent effect that was discernible. The symptoms were similar to those of early pregnancy, and although the patients generally asked to be permitted to stop taking the tablets, they did not feel that they had been harmed by the medicine.

With ethinyl estradiol, seven of the patients in this study (14 per cent) had a true toxic reaction. During the treatment of 109 patients reported in five papers,[9, 12-14, 16] there were 13 reactions (11 per cent toxicity). Kurzrok, Birnberg and Livingston[15] gave ethinyl estradiol to 59 patients after delivery to prevent lactation. In their series there was no evidence of toxicity. Of course, it is a well-known fact that patients who have recently been pregnant tolerate large doses of estrogenic substances.

It was interesting to note that the optimum daily dose of ethinyl estradiol in this series was low (0.05 mg. to 0.1 mg.). According to the literature, most of the treatment was with doses of 0.3 mg. to 0.45 mg. The puerperal cases were given up to 2.4 mg. However, in two of the papers, the effective dose was considered to range from 0.05 mg. to 0.15 mg.

The three estrogens that produced a greater response in the patient were believed to be less affected by the liver. The other estrogens going through the portal circulation did not reach the general circulation in sufficient concentration to be very beneficial. However, sublingual administration was shown to be very much more effective.[19] It is believed that this method of administration, like the hypodermic injection, puts the hormone into the general circulation without its first having to pass through the liver, where it is partly inactivated.

Summary

Ethinyl estradiol was the most potent oral estrogen used up to the present time. Satisfactory relief of hypo-ovarian symptoms was usually obtained with 0.05 mg. to 0.1 mg. daily although larger doses were occasionally necessary. Its effect was compared to that of alpha-estradiol and to estrone, estradiol benzoate, diethylstilbestrol dipropionate and conjugated estrogens-equine previously studied. Of this group, ethinyl estradiol and diethylstilbestrol dipropionate caused mild toxic reactions in an occasional patient without apparent permanent harm. Keeping the dose down to the minimum needed for maximum effectiveness reduced the toxic symptoms. The addition of the ethinyl radical greatly increased the effectiveness of alpha-estradiol, thus reducing the cost of treatment. The oral method of treatment had many advantages.

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947 WEST EIGHTH STREET

HYSTEROSALPINGOGRAPHY, A ROUTINE AID IN GYNECOLOGICAL DIAGNOSIS

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VISUALIZATION of the female genitalia in a group of fifty-two selected patients has proved a practical and innocuous procedure by which a more accurate knowledge of numerous pelvic conditions was obtained. The simplicity and clinical safety of hysterosalpingography with the use of the recently introduced opaque medium, Viscorayopake, warrant its adoption, routinely, for both office and hospital use.

Many pathologic growths of the female generative tract were clearly defined by this method and, in many cases, unsuspected lesions were revealed. The alteration in size and contour of the uterine shadow indicates not only the extent and location of new growths, but also identifies the type of tumor by means of characteristic and representative patterns. Since the length, course and patency of the Fallopian tube, as well as the presence of new growths, can be determined by x-ray, problems of sterility lend themselves particularly to its use. When employed with tubal insufflation as described by Rubin[1, 2] complete knowledge as to both structure and function of the tube is obtained. In certain instances, tenuous peritubal adhesions causing obstruction to ovular migration, may undergo lysis following passage of the viscous radiopaque fluid. Salpingography served not only to differentiate between intrapelvic masses, but also between abdominal tumors from those of pelvic origin. In my experience, this test has often been a guide to correct operative procedure and surgical conservatism.

The stereoptical roentgen technique in hysterography was also utilized to advantage. By this method, the relative intrapelvic position and size of anatomic structures and growths were determined, rendering an expressive picture in all dimensions.

Since 1910, when Rindfleish[3] first introduced hysterography, many media have been used by various investigators. Lelorier,[4] W. H. Carey,[5] I. C. Rubin,[6] W. T. Kennedy,[7] J. A. Sicard,[8] T. Neustaedter,[9] and P. Titus[10] have contributed largely to the development of hysterosalpingography in the past three decades. The radiopaque substances[11, 12] such as Collargol,[13] halogen salts, Lipiodol,[14] Iodopine, iodized oils[6] and the crystalline iodine compounds, Uroselectan,[15] Diodrast[16] and Hippuran,[17] proved disadvantageous for clinical usage. These were eventually discarded because of various shortcomings, such as (1) unsatis-

*The opinions and assertions contained in this paper are the personal ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

factory opacity, (2) tissue irritation, (3) foreign body reaction due to retarded absorption, (4) insufficient viscosity, (5) toxicity and (6) chemical instability.

In the present studies, the fluid substance, viscorayopake,* was used. First introduced for clinical trial by I. C. Rubin[16] at the Mt. Sinai Hospital, New York City, in 1941, it has fulfilled the requisites for an adequate and satisfactory opaque medium for pelvic x-ray. Nontoxic, quickly absorbed, chemically stable and amply viscous, it is easily administered, and does not gel or crystallize at room temperatures.

Method

This test may be employed in any properly equipped office or hospital. The technique is uncomplicated and safe. The patient is given two drams of licorice powder the night before and an enema on the morning of the test. The patient is placed on a Squier genitourinary x-ray table in lithotomy position, and a bimanual examination is performed to determine the cervico-uterine angle (for direction of canal) and the fundal size (for estimation of its capacity).

Aseptic technique is observed. The vulva and vagina are thoroughly cleansed with soap and water and the patient is draped with sterile towels.

The cervix, visualized through a nonopaque, bivalved speculum, is wiped dry and the external os is painted with tincture of iodine. A tenaculum forceps may be applied, but I found no advantage in this painful procedure, except in cases requiring traction for better cervical exposure, or, for a stenotic cervix resisting insertion of the cannula, or, where pressure against the cannula guard was necessary to prevent leakage.

A 20 c.c. syringe, containing 15 c.c. of viscorayopake,[19] is fitted by means of a Luer metal tip to a uterine stem cannula with perforated end (as used in the Rubin insufflation test), or, when desirable, to a Colvin[20] cervical stainless steel screw-tip cannula. The latter eliminates the danger of uterine perforation and, in some cases, has been found satisfactory in preventing backflow. Upward pressure of the syringe piston displaces air from the syringe and its contained opaque fluid. If the medium injected into the uterine cavity contains air bubbles, errors in diagnosis are prone to occur. The cannula is then cautiously inserted through the external os, following the line of the cervico-uterine axis, until the perforated tip lies within the cavity. If the Colvin device is used, the screw-tip is rotated until it becomes firmly fixed in the cervical canal.

Excessive traction, or upward pressure on the cervix may cause uterine displacement producing shadow overlapping of the cavity outline. It is therefore advisable, before x-rays are taken, to replace the fundus so that it lies in a plane somewhat parallel to the x-ray plate.

With the cannula held in the cervix, the patient is moved into proper position under guidance of the x-ray technician, so that the x-ray tube and plate are in proper alignment with the pelvis.

I have used, ordinarily, for a 20-centimeter body thickness, 50 milliamperes and 58 primary volts for a two-second exposure with the focal plate distance between thirty and thirty-six inches.

*Chemical structure: Diethanolamine salt of 2, 4,-dioxo-3-iodo-6 methyl tetrahydropyridine acetic acid. Three and one-half per cent concentration of polyvinyl alcohol is added to procure satisfactory viscosity.

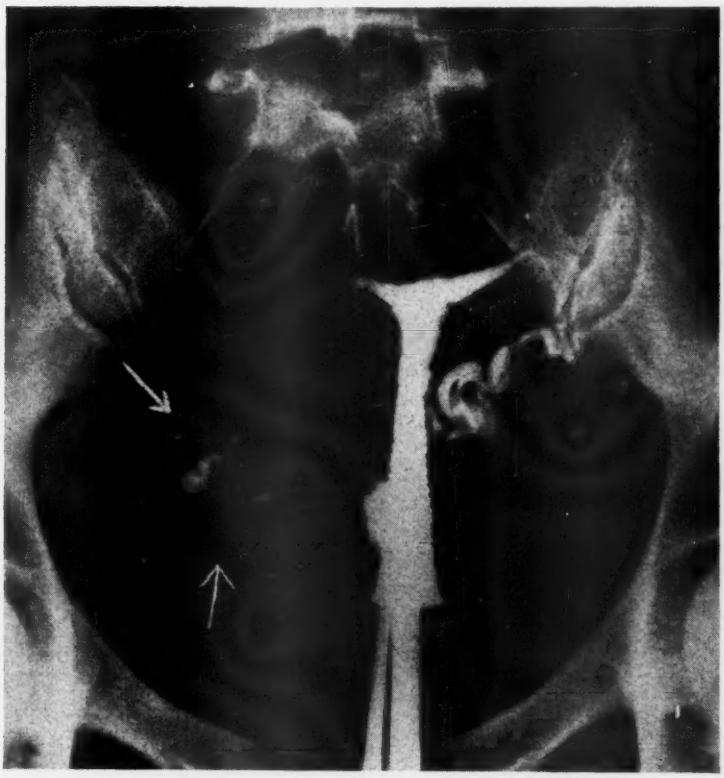

Fig. 1.—Hysterogram showing unilateral tubal patency and small uterus. Note left pelvic lipiodol shadows appearing also in the original flat plate, or secret film.

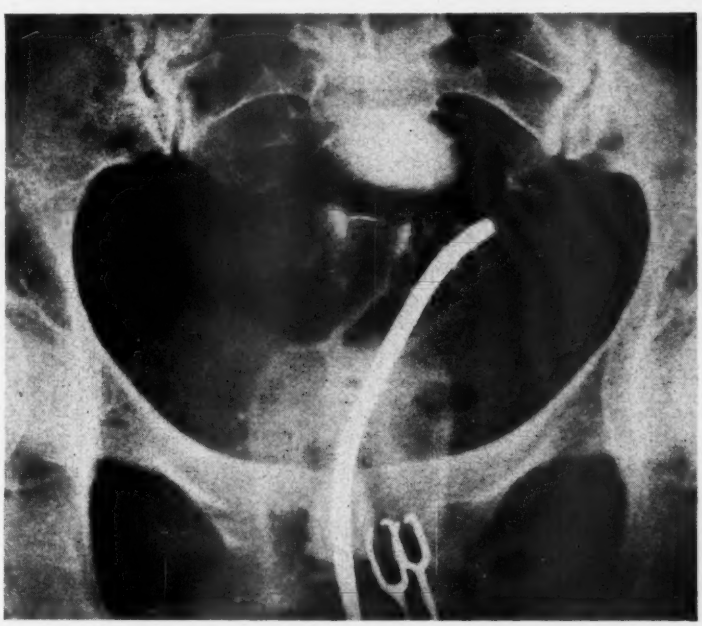

Fig. 2.—X-ray film of a submucous fibroid delineated by viscorayopake and carbon-dioxide contrast media.

A flat plate or scout film is first taken. This often reveals calcified lymph nodes, phleboliths, or unabsorbed lipiodol used in previous tests, and is of value in excluding misleading shadows (Fig. 1). Two c.c. of radiopaque fluid are then injected very slowly, and a second plate is taken. By delivering the viscous medium into the uterine cavity very gradually, with light or moderate pressure, the patient is spared unnecessary pain. Two c.c. injections are repeated until 6 or 8 c.c. of viscorayopake and four or five x-ray films have been used. At this point, the fluid contents of the uterine cavity may be removed by withdrawing the piston.

The syringe is disconnected from the cannula, and about 10 to 15 c.c. of CO_2 gas, from a second clean syringe, are then injected into the uterine cavity. Another plate is taken while piston pressure is maintained. Hysteroaerography[17] delineates cavity and tumor outlines by contrast of the gas with the viscorayopake film adherent to the uterine wall (Fig. 2). Contrast media provide additional means for obtaining more accurate x-ray plates.

Two c.c. of fluid are the optimum quantity used for any single injection; this amount is sufficient to render progressive silhouette changes required for comparative serial-film studies. Enlarged uterine cavities or tubal dilatations sometimes require up to 15 c.c. of opaque medium. In one instance of uterine cavity enlargement due to fibroids, 24 c.c. were injected without deleterious effect. (Fig. 3.)

A forty-five minute follow-up x-ray picture will very often show the excretion of the opaque fluid in the renal tract as well as its partial or complete absence from the pelvis (Fig. 4). Absorption and excretion of viscorayopake are rapid.

With each injection, the patient was asked to point with a finger to areas of discomfort or pain, and as the medium traversed the uterine cavity and the patent tubes, the finger moved laterally from the suprapubic midline. Patency, as well as the location of tract obstruction, was often clinically predetermined in this way.

The patient sits up within fifteen minutes after the last injection, and, in most instances, is immediately ambulatory. Transitory nausea and vomiting were observed infrequently among the entire group of fifty-two patients. Thirty-two women, or sixty-one per cent, were entirely free of discomfort or pain during or after the injections. Fifteen, or twenty-nine per cent, complained on questioning, of either discomfort, or mild but bearable pain, and five, or ten per cent, manifested severe and painful reactions, lasting from forty-five minutes to twenty-six hours. Two of these patients were relieved by codeine sulfate, while sedation, bed rest and a heating pad were sufficient to control the symptoms in the remaining three instances. In eight patients, or fifteen per cent, the application of the tenaculum, or traction on the cervix caused pain.

In two patients with a history of childhood convulsions and syncope, a definite *petit mal* syndrome occurred following the second injection. In both instances, however, recovery was immediate and there were no sequelae.

Where marked nervousness or apprehension is present, mild sedation should be used in preparation for the test.

Acute pelvic diseases, gonorrhea, intrauterine or ectopic pregnancy, cervical carcinoma or infection, and epilepsy contraindicate the use of hysterosalpingography. It is wise to postpone the test until after the

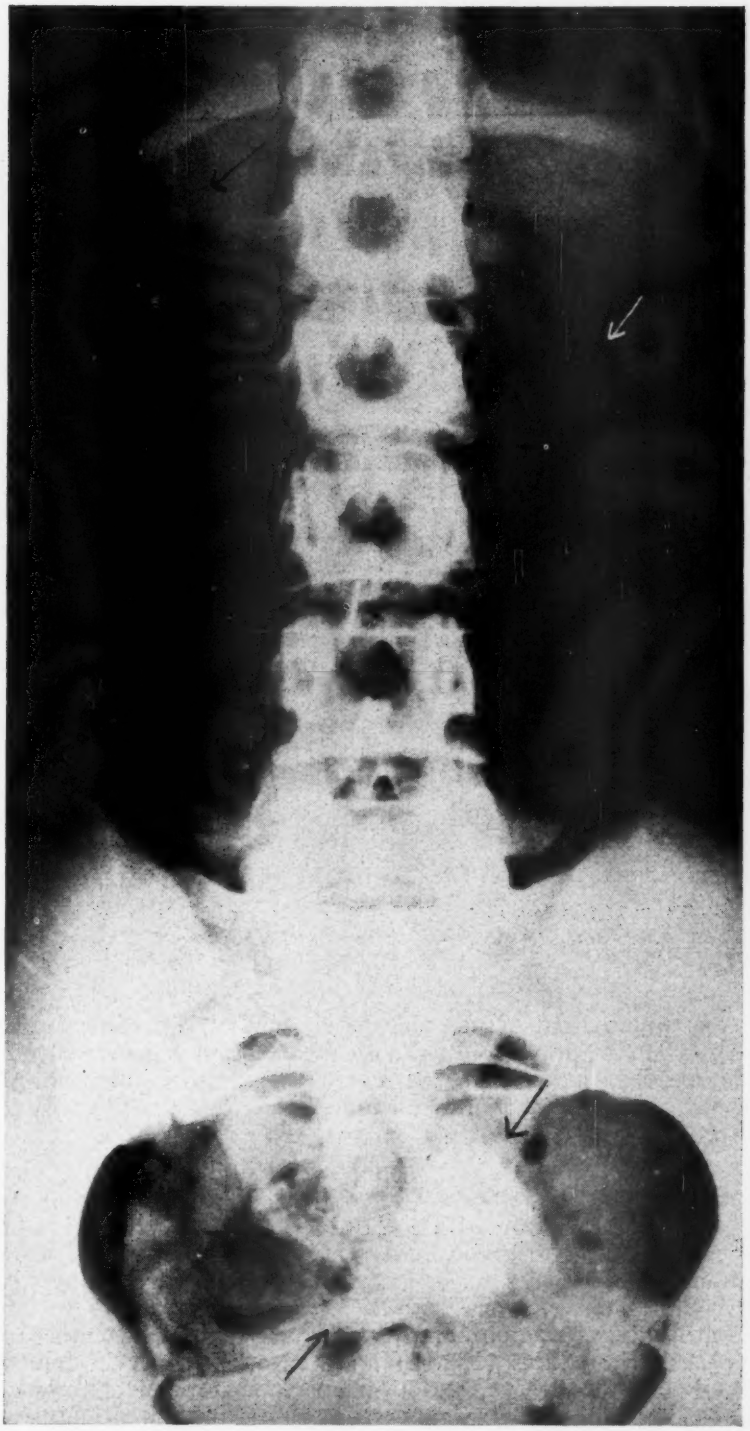

Fig. 3.—Broad shadow concavity in left uterine wall indicating submucous fibroid invading uterine cavity.

menstrual or ovulatory phase, and for a six-month post-partum, and at least a thirty-day postoperative period.

Although indicated for the study of abnormal bleeding, such as menorrhagia, metrorrhagia and staining, the procedure was employed only during the phase of recession of active bleeding.

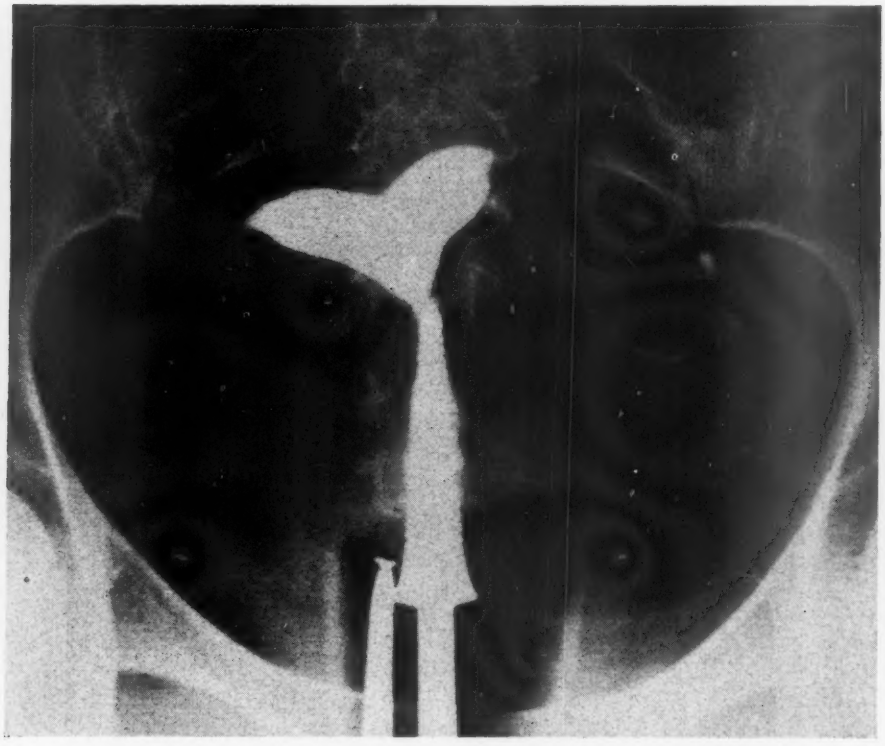

Fig. 4.—X-ray evidence of renal excretion of viscorayopake showing bilateral ureteral shadows thirty minutes after the final intrauterine injection. Note residual dye in the pelvis.

In the examination of palpable pelvic masses, dysmenorrhea or obscure pelvic pain, additional valuable information was very often made available. This method proved worth while also in determining the structural status of the Fallopian tube, particularly in patients treated for sterility.

Results

Thirty-eight women were x-rayed routinely in the course of sterility studies, after insufflation with the Rubin apparatus and technique had been performed. Numerous interesting and varied uterine anomalies and tumors, as well as unsuspected tubal disease resulting in canal closure and distortion, were found.

Infantile uterus was observed twice: one showed incomplete fusion of the Müllerian ducts (Fig. 5) and the other a cervix four inches long. Bicornuate uterus, and ovarian cyst, respectively, were diagnosed twice. Eight sterility patients had tubes which, although patent, showed marked curling, dilatation and partial obstruction due probably to peritubal adhesions. These conditions, commonly recognized as possible underlying causes of sterility, are very often not detected

on bimanual examination. Their unexpectedly high incidence emphasizes the importance of x-ray as a routine measure to be used in conjunction with the Rubin insufflation test.

Findings by both methods were invariably in agreement, although, in one instance in which a preliminary insufflation indicated tubal closure, x-ray revealed bilateral patency. Moreover, in another instance, a repeated hysterogram disproved cornual obstruction observed in previous x-ray films. On these rare occasions, a physiological contraction or spasm of the uterotubal sphincter muscle may take place,[21] and a conclusive prognosis therefore should be reserved until at least several confirmatory x-ray studies have been made.

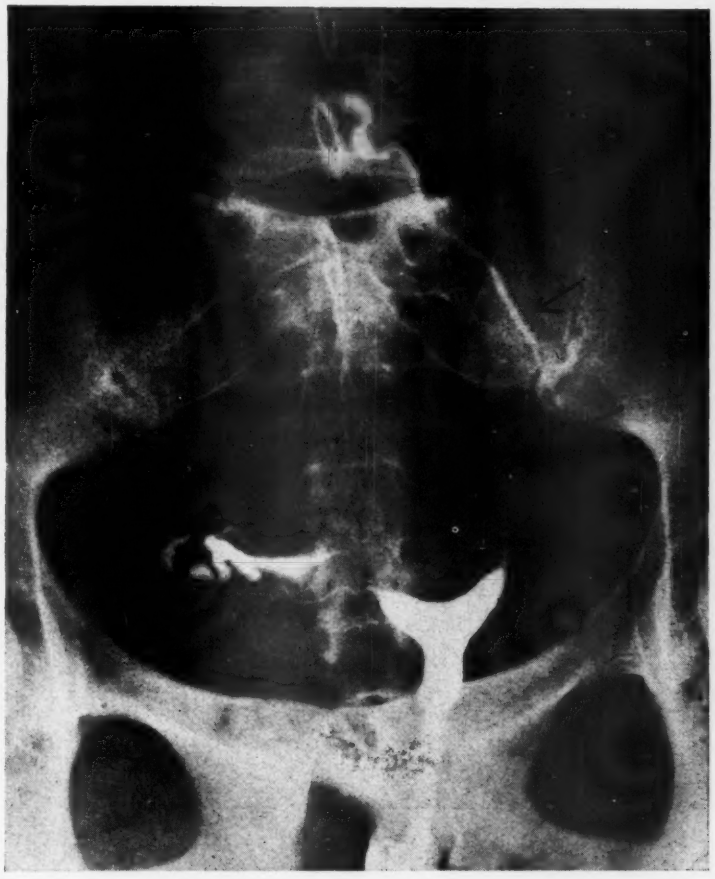

Fig. 5.—Bicornuate uterus and one patent tube demonstrated by viscorayopake.

Among thirty-eight sterility studies, tubal patency in one or both tubes was demonstrated twenty-seven times. In fifteen instances, both tubes were open, but in eight of these women, there were varying degrees of kinking and dilatation. In twelve patients, only one tube was visualized as patent. Among these, there were four postoperative cases in which the unilateral absence in x-ray films was verified by reports of salpingectomy received from the attending surgeons: in one of these a short tubal stump was visualized. In the remaining eight in-

stances of unilateral obstruction, five occurred proximally, two centrally, and one at the distal end (Fig. 6).

Bilateral closure occurred at the fimbriated portion in three instances, centrally in two, and proximally, at the uterotubal junction in six instances. Of the latter, three must be assumed to have been patent, since x-rays were unwittingly taken during already existing pregnancies. Two of these women, with long-standing amenorrhea, had been previously insufflated, and were six weeks gravid (Fig. 7), while the third was an obese, eight-month amenorrheic patient of menopause age (44 years), in whom an eighteen-week fetus was revealed on x-ray. All three gravidities continued uninterruptedly and were delivered at term of normal babies. The constancy in x-ray of cornual closure in all three gravidities gave rise to the query as to whether uterine gestation affects, or coexists with a physiological contraction of the uterotubal muscle.

Fig. 6.—Extrapelvic ovarian cyst diagnosed by presence of displaced course of Fallopian tube shadow.

Pathologic findings, predetermined correctly in most instances by pelvic examinations, were also studied by radiography in the remaining fourteen patients. In each case, further knowledge was obtained, and, several times, planned surgical procedures were changed because of the x-ray findings. The stereoscopic technique proved valuable in determining not only the exact position but the relative size of the tumors.

There were six fibroids, four ovarian tumors, two hydrosalpinx (Fig. 8), one uterine polyp and one multiple carcinoma of the uterus and tube. Menometrorrhagia was the chief complaint in all these women.

There were four submucous fibroids (Fig. 3) and two cases of fibroid uteri in which the cavity was not invaded. Tubal displacement characterized the latter films.

Two ovarian cysts were intraligamentous, and in one instance, in which the diagnosis of a "large subserous fundal fibroid" was made at another hospital, our x-ray findings (Fig. 6) revealed a unilateral ascending linear shadow, which corresponded to the canal of the tube displaced cephalad by an extrapelvic ovarian tumor. The histologic report was serous cystadenoma of the ovary.

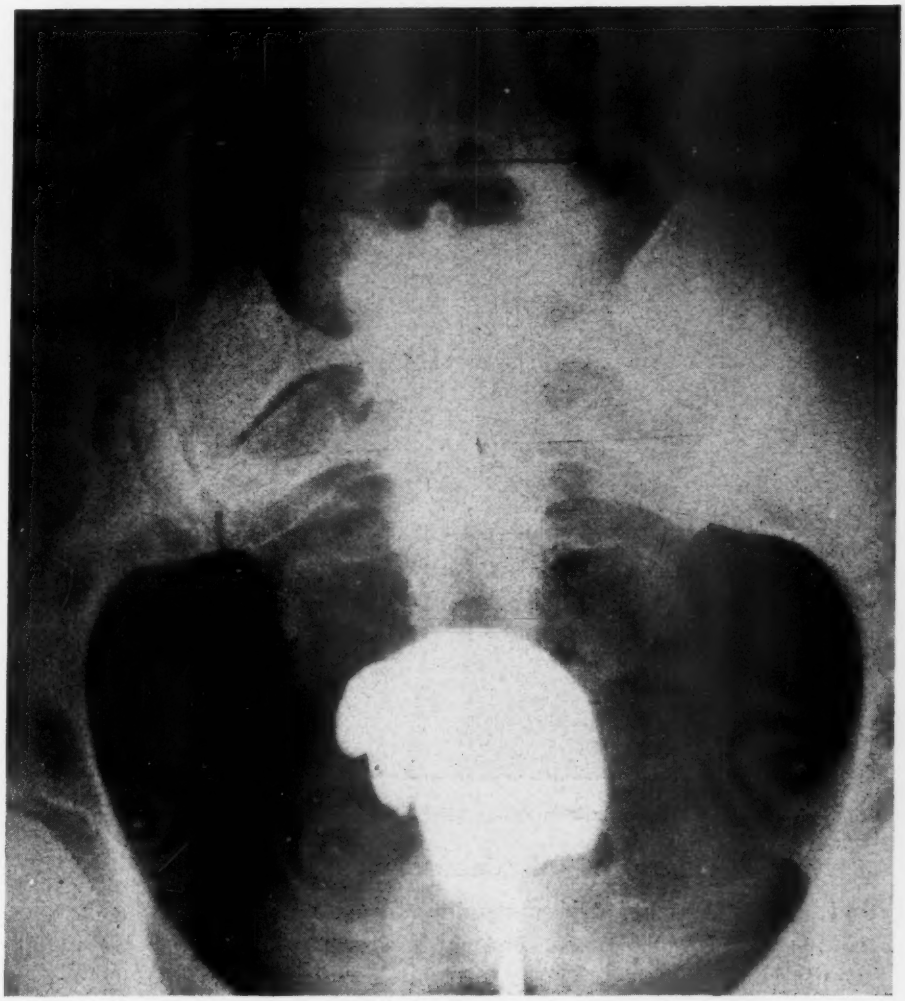

Fig. 7.—Hysterogram of clinically unrecognized early pregnancy showing bilateral obstruction at the uterotubal sites.

In both cases of hydrosalpinx, the x-ray findings were more clearly diagnostic than bimanual pelvic examinations.

At curettage, a small clinically unrecognized uterine polyp, causing menopausal bleeding was removed after hysterogram revealed its presence.

In an obese, sixty-two-year-old woman, with metrorrhagia, discharged recently from another hospital with a diagnosis of "abdominal tumor, inoperable," hysterography revealed a double lesion, namely, a uterine carcinoma, and an abnormally large intra- and extrapelvic tubal shadow, which, at operation, was found to be a huge tubal carcinoma. Here, preoperatively, the otherwise unrecognizable pelvic origin of an abdominal mass was ascertained.

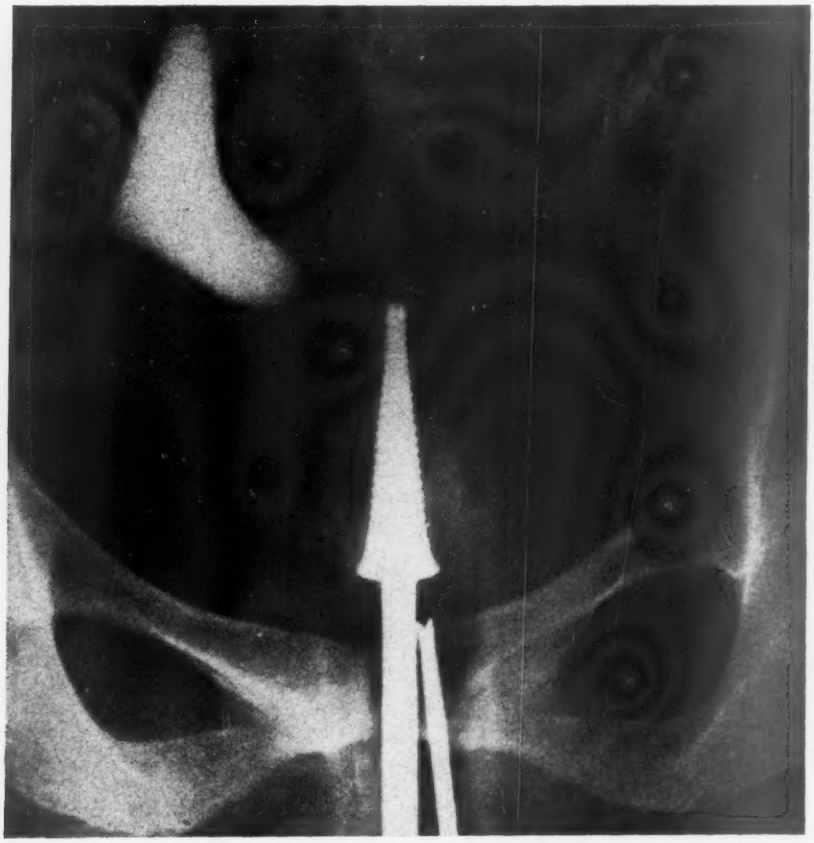

Fig. 8.—Hysterosalpingogram showing bilateral pyosalpinges in a sterility patient.

Conclusion

1. Viscorayopake, a recently introduced opaque fluid, has proved eminently satisfactory for clinical use in x-ray study of the female genitalia.

2. Hysterosalpingography was employed in fifty-two patients with gynecological disorders. These included pelvic tumors, pain, uterine bleeding, dysmenorrhea and sterility. In the sterility studies, it proved valuable in conjunction with the Rubin insufflation test.

3. Information as to the size, location and type of intra- and extrauterine growths, as well as the structure and patency of the Fallopian tube, was obtained. The x-ray differentiation between uterine and

ovarian tumors, as well as abdominal and pelvic growths, was of noteworthy diagnostic significance. The high incidence of unsuspected lesions in sterility studies was remarkable.

4. The facility and safety of the technique and the simplicity of the x-ray film interpretation warrant its use as a diagnostic routine measure in both hospital and office.

5. The technique for the test is described. Contraindications and indications for its use and the advantages and pitfalls inherent in the procedure are noted. Clinical sequelae are also mentioned.

6. The constant x-ray evidence of tubal closure in three pregnant patients may indicate that a uterotubal sphincter spasm occurs physiologically in the gestational state.

7. Findings are statistically presented with reproductions of interesting x-ray films.

8. A brief history of hysterography is included.

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VALIDITY OF TWO-HOUR RAT TEST FOR HUMAN PREGNANCY*

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TWO biologic tests for the determination of early pregnancy have come into general use, the Aschheim-Zondek (mouse test) and the Friedman modification (rabbit). The accuracy of these tests is very good, but the length of time required of 96 and 36 hours, respectively, is one of the drawbacks. Frank and Berman[1] described a 24-hour pregnancy test, using rats; Crew[2] and Weisman, Snyder and Coates[3] published procedures using Xenopus laevis (toad) for pregnancy diagnosis in which results were obtainable within 4 to 18 hours. Later in 1942, U. J. Salmon, S. H. Geist, A. A. Salmon and I. L. Frank[4] published an interesting paper describing a six-hour pregnancy test using immature rats, and subsequently published an abstract[5] stating 96 per cent accurate results were obtainable within two hours.

The test described by Salmon, et al.,[5] seemed to satisfy the needs for a practical, rapid test, so we endeavored to determine the reliability of the two-hour rat test for ascertaining human pregnancy.

A series of tests was performed on urine samples as follows:

1. For pregnancy diagnosis
2. For known conditions of nonpregnancy

Our findings showed the test to be not only positive for conditions of pregnancy, but also for women undergoing menopausal changes, for women at midmonth primarily, for males anticipating coitus, and male and female subjects after coitus.

Material and Methods

Over 360 urine specimens were tested on over 1,000 immature female Wistar albino rats for color reaction, to determine pregnancy and nonpregnancy conditions. The urines for the pregnancy tests were supplied chiefly through a laboratory specializing in performing the Friedman rabbit test. The results of the Friedman test obtained in the laboratory of Dr. Frederick Langner were compared with the two-hour rat test findings, and clinical diagnosis secured in any cases in which results were doubtful.

We used the two-hour rat test described by Salmon et al., in most instances, and repeated occasionally with the four- to six- or twenty-four-hour test. A hooded strain of rats was also tested, but the ovaries showed normally positive pink to red color without treatment of any sort, and therefore this strain was discarded as unsatisfactory. For the test, at least two immature female Wistar albino rats of known age and weight (ages 22 to 33 days, and 30 through 45 grams) were each

*This investigation was aided by a grant from the Samuel S. Fels Fund.

injected subcutaneously with 2 c.c. of specimen of urine. At the end of the desired hour, the rats were gassed individually in a closed chamber for about two and one-half minutes, until dead, and the ovaries exposed and examined. The ovary was usually lifted out of the abdominal cavity by means of a small hook, to avoid changes in circulation. Negative ovaries appeared uniformly pale and cream colored. Positive ovaries had a definite blush to strong red color. To eliminate incorrect and impressionistic readings, the ovaries were read promptly upon exposure, then compared with colors on a scale. Satisfactory positive colors were secured for comparison purposes by using a hemoglobin scale (Tallqvist) from 60 per cent up. However, the confusing negative colors could not be identified on the Tallqvist scale, so a simple color scale was designed for reading various negative and positive shades of ovarian reaction, based on the Munsell color chart system.

Results

In Table I is a summary of the tests for diagnosis of conditions of pregnancy. In 61 subjects both the two-hour rat test and the rabbit test were in agreement. There were 46 positive tests for pregnancy, and 15 negative reactions. The rat test was likewise in agreement for the six-hour and twenty-four hour period.

In 11 subjects, with age range of 40 to 56 years, there was practically no agreement between the two-hour rat test and the rabbit test. The two-hour rat test was positive in 11 tests, while the rabbit reaction was negative in 10 of the 11 tests. The clinical diagnosis indicated menopausal difficulties in all cases, and physicians confirmed the diagnosis in all cases at a later date as nonpregnant. The positive reaction in the two-hour rat test often faded to negative in the six and twenty-four-hour tests.

In eight other subjects, with age range of 19 through 46 years, there was a marked disagreement in the results of the two-hour rat test and the rabbit test. Nine of the two-hour rat tests were positive, while only one of nine tests was positive for the rabbit test. The clinical diagnosis proved the two-hour rat test to be more accurate in these subjects, for six of the subjects were pregnant and one not pregnant. One of the subjects was diagnosed as insane, and was not pregnant. The two-hour rat test was apparently more sensitive than the rabbit test, for several of the same subject's specimens became positive when repeated on samples secured approximately a week later. This was further confirmed by the fact that a known pregnancy of day age 41 proved definitely positive in the two-hour rat test and only weakly positive in the rabbit test. On day 44, a specimen from the same woman was read as only moderately positive in the rabbit test.

Male urine served frequently for control injections, and on one particular occasion it was observed the specimen was markedly positive in reaction, an unusual occurrence. It was finally determined the only factor that could explain the change was coitus the previous evening. This observation was confirmed, and suggested a series of studies on color reactions accompanying sexual excitement.

In Table II are summarized the results of the reactions accompanying sexual excitement in three male and three female subjects. The 42 male samples tested on 66 rats (the two-hour rat test) showed five positive and one negative reaction one hour before anticipated evening coitus. The control specimens secured the morning of the scheduled evening

TABLE I. COLOR TEST FOR PREGNANCY

ALL SAMPLES OF UNKNOWNS				RABBIT TEST RESULTS	RAT TEST RESULTS			CLINICAL DIAGNOSIS
	NO. OF SUBJECTS	NO. OF SAMPLES	NO. OF RAT TESTS		2 HOURS	4 TO 6 HOURS	24 HOURS	
A. Agreements (with rabbit tests)	61 (Age 19 to 40 years)	61	78	46 Pos. 15 Neg.	46 Pos. 15 Neg.	4 Pos. 4 Neg.	7 Pos. 1 Neg. 2 Pos.	
	2	2	2					
B. Disagreements 1. Menopause	11 (Age 40 to 56 years)	11	19	1 Pos. 10 Neg.	11 Pos.	3 Pos. 1 Neg.	1 Pos. 2 Neg.	Menopausal
2. Clinical Diagnosis vs. Laboratory Diagnosis	7 (Age 19 to 46 years)	8	8	8 Neg	8 Pos.			5 Pregnant 1 Not pregnant
	1 (Age 38)	1	1	Pos.	Pos.			1 Insane (Not pregnant)

event showed four positive and eight negative responses. The aftercoitus specimens showed four positive and one negative within one hour, eight positive and one negative within four hours, and six positive and five negative within eleven hours.

TABLE II. COLOR TESTS FOR NONPREGNANCY CONDITIONS

REACTIONS ACCOMPANYING SEXUAL EXCITEMENT						
NO. OF SUBJECTS	NO. OF SAMPLES	NO. OF RAT TESTS	CONDITION OF EXPERIMENT	RAT TEST RESULTS		
				2-HOUR	6-HOUR	24-HOUR
3 Males	42	66	Coitus			
			Before (P.M.)			
			Within 1 hour	5 Pos.		1 Pos.
				1 Neg.		2 Neg.
			After			
			Within 1 hour	4 Pos.	1 Pos.	1 Neg.
				1 Neg.		
			Within 4 hours	8 Pos.	1 Neg.	5 Pos.
				1 Neg.		2 Neg.
			Within 11 hours	6 Pos.		2 Pos.
				5 Neg.		3 Neg.
3 Males	11	17	Control (A.M.)	4 Pos.		2 Pos.
				8 Neg.		3 Neg.
3 Females	50	77	Coitus			
			Before			
			A.M.	2 Pos.		1 Pos.
			(Cycle days 11, 13, 15)	1 Neg.		
			(Cycle days 10, 16 to 21)	2 Pos.		1 Pos.
				1 Neg.		
				2 Doubtful		
			Within 1 hour (P.M.)	1 Pos.		1 Neg.
			(Cycle days 11, 12 and 13)	3 Neg.		
			(Cycle days 9, 23 and 24)	3 Neg.		
			After			
			Within 1 hour	2 Pos.		1 Pos.
			(Cycle days 12, 13, 17 and 23)	2 Neg.		1 Neg.
			Within 4 hours	9 Pos.	1 Pos.	4 Pos.
			(Cycle days 9, 11 to 13, 15 and 23)			3 Neg.
			Within 11 hours	10 Pos.	1 Pos.	5 Pos.
			(Cycle days 9 to 14, 16, 20, 24 and 25)	11 Neg.	1 Neg.	7 Neg.
				1 Doubtful		

In fifty samples of three females tested on 77 rats, the two-hour rat test showed on the morning of the day of anticipated coitus two positive, four negative, and two doubtful reactions during the safe period (days 9, 10, 16 to 24), and three positive and four negative during unsafe period (days 11, 12, 13 and 15). The aftercoitus specimens showed responses quite similar to the male, namely, two positive and two negative within one hour, nine positive within four hours, and eleven positive, eleven negative and one doubtful within eleven hours. The six and twenty-four-hour rat tests showed that a positive two-hour rat test may remain positive or fade, to become negative.

In Table III are summarized the daily reactions on three complete cycles on samples of three unmarried women. In the 81 samples tested on over 109 rats, there were positive reactions usually three days in succession during the midinterval. Positive reactions occurred also one

TABLE III. COLOR TEST FOR NONPREGNANCY CONDITIONS

NO. OF SUBJECTS	NO. OF SAMPLES DURING CYCLE	NO. OF RAT TESTS	INDIVIDUAL	LENGTH OF CYCLE	SUMMARY OF REACTIONS	DAILY REACTIONS ON THREE COMPLETE CYCLES — DAY OF CYCLE (TWO-HOUR RAT TESTS)																													
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	24	36	N. M. (23 yr.)	26	7 Pos. 17 Neg.	+	0	0			0	+	0	0	0	0	0	+	+	+	0	0	0	0	+	0	0	+	0	0	0					
1	31	34	E. Y. (31 yr.)	31	9 Pos. 21 Neg. 1 Doubtful	+	+	0	0	0	0	0	0	0	0	0	+	0	0	+	+	+	0	0	0	0	+	0	0	0	0	0	0	?	+	+
1	26	39	J. E. (23 yr.)	29	4 Pos. 22 Neg.	0	+	0	0	0	0			0	0	0	0	0	0	0	+	+	+	0	0	0	0	0	0	0		0	0	0		
3	81	109																																	

Note:

In three complete cycles, there were a total of 12 positive, 60 negative and 1 doubtful reactions on days other than the 9 positives of the midperiod.

Results of 6-hour rat test: 3 Positives in 19 tests.

Results of 24-hour rat test: 1 Positive in 9 tests.

TABLE IV. COLOR TEST FOR NONPREGNANCY CONDITIONS

REACTIONS DURING MIDPERIOD					DAY OF CYCLE (2-HOUR RAT TEST RESULTS)									
NO. OF SUBJECTS	NO. OF SAMPLES	NO. OF RAT TESTS	INDIVIDUAL	LENGTH OF CYCLE	10	11	12	13	14	15	16	17	18	19
8 Females	93	124	N. M. (23 yr.)	28		0	0	+	+	+	+	0	0	0
				26	0	0	0	+	+	+	0	0	0	0
				32		0	0	0	+	0	+	0		
			E. Y. (31 yr.)	28						0	+	+	+	0
				31	0	0	+	0	0	+	+	+	0	0
			J. E. (23 yr.)	32			0	0	+	+	+	0		
				29	0	0	0	0	0	0	+	+	+	0
				29		0	0	0	0	+	?	0		
			D. K. (19 yr.)	42				0	0	+	+	+	0	0
				30					0	0	+			
			H. DeW. (20 yr.)	32						+		+	+	0
			L. A. F. (34 yr.)	31					+	+	0	0	0	
			D. T. T. (28 yr.)	29			0	0	0	0	+	0		
			E. F. M. (26 yr.)						0	0	+	0	0	
				31 days ave.	3 Neg.	6 Neg.	1 Pos. 6 Neg.	2 Pos. 7 Neg.	5 Pos. 7 Neg.	8 Pos. 6 Neg.	10 Pos. 2 Neg. 1 Doubtful	5 Pos. 8 Neg.	3 Pos. 6 Neg.	7 Neg.

Results of 6-hour rat test: 3 Pos. 19 Neg.

24-hour rat test: 1 Pos. 8 Neg.

(Miss E. H., Aged 24) Pos. (Cycle days 15 to 17 19 to 23)

(Subject abnormal receiving medical treatment.)

day during menstruation, as well as late in the cycle. The positive two-hour rat test has great tendency to fade if read at six or twenty-four hours.

In Table IV are summarized reactions during midperiod of the cycles in eight women. In the fourteen cycles that averaged 31 days in length, the 93 samples tested on 124 rats showed positive reactions usually for three successive days, the greater number occurring on days 14, 15, 16 and 17, with range of days 12 through 18. The two-hour positive reaction has great tendency to fade out to negative during the six and twenty-four-hour tests in the midperiod samples.

Discussion

It is unfortunate that the two-hour rat test proved positive in conditions other than pregnancy. For individuals up to thirty-seven years of age, the two-hour rat test may prove satisfactory for pregnancy diagnosis, but it would be advisable, when reactions are relatively weak, to confirm with the 24-hour rat test.

The two-hour rat test, when used with the color scale, offers new possibilities for indication of hormone output. The test has been used with some success for establishing probable time of ovulation for insemination purposes. In Table IV one subject (D. T. T.) had only a single positive reaction at midperiod interval, rather than the usual three positive days. This subject has to date been unable to conceive successfully, in contrast to some others tested, and this finding suggests the lack of the hormone essential in normal process of ovulation.

Table III indicates women are cyclic in nature, as determined by occurrence of positive reactions during midperiod interval, during menstruation, and again late in the cycle. Farris[6] reported a cyclic pattern of activity in women, with a definite increase in walking at the three periods of the cycle, when the two-hour rat test became positive. In contrast, the male is noncyclic, and is apparently stimulated to produce sufficient hormone to cause a positive reaction even when anticipating coitus.

Table II shows both men and women have positive reactions postcoitus. This finding suggests a possible explanation regarding certain normal couples desirous of having children, without success. The usual sexual history of such couples indicates that coitus occurs much more frequently than in the usual successful couple. Is it possible that the stimulation of frequent coitus produces an excess hormonal output in the female to offset the normal, rhythmical hormonal balance? This theory is being tested.

Summary

The two-hour rat test was not found to be specific for diagnosis of pregnancy.

The two-hour rat test gave positive color reactions in nonpregnancy conditions as follows:

a. In women undergoing menopausal changes.

b. In normal women for three successive days during mid-interval of cycle, with range from the twelfth through the eighteenth day.
c. In normal women on single days, usually during menstruation and again late in cycle.
d. In men and women after coitus.
e. In men anticipating coitus.
f. In one woman with hydatidiform mole.
g. In one woman with clinical diagnosis of insanity.

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STATUS OF INFANT AT BIRTH AS RELATED TO BASAL METABOLISM OF MOTHER IN PREGNANCY*

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WHAT relationship exists between a woman's basal metabolic rate and the birth weight of her infant? Do disturbances of maternal thyroid function affect the growth pattern of the fetus? How imperative is it that "hypothyroid women" be fed thyroid during pregnancy? Is it possible to control the "obesity" of the fetus by feeding thyroid gland to the mother during pregnancy? These and numerous corollary questions are repeatedly asked and answered in medical literature. Unfortunately, the answers are often equivocal, in some instances definitely conflicting. We shall consider here certain of the controversial questions regarding the relationship of thyroid function during pregnancy to the status of infants at birth and during the first six months of life.

We have very carefully collected, at the Fels Research Institute, several hundred basal metabolism readings in various stages of pregnancy and on the same women in a nonpregnant state. Furthermore, we have extensive data on the physical state of infants of these mothers and on their growth progress for a number of years. In this communication we shall therefore present the results of the examination of this data together with such conclusions as seem warranted.

Method of Study

Basal metabolic rates on 163 women in the last month of pregnancy, as well as data on the gain in basal metabolic rate from the beginning of pregnancy to the ninth month, were used in the present study. All basals were done in duplicate by the indirect method. Only subjects who live within a short radius of the Institute were included, and an adequate pretest rest period was required. Most patients have anywhere from six to twenty-four basals taken here over the course of and following their pregnancies, so that the inaccuracies often encountered as a result of apprehension or poor preparation were largely eliminated. Mothers were divided in groups of "high," "intermediate," and "low" ninth month basals, and "high," "intermediate," and "low" B.M.R. gain during pregnancy.

Measurements and x-rays of infants were made at birth, and subsequent growth and development carefully followed by members of our staff. The following items were used in the present study:

*We wish to express our appreciation for the contribution in terms of data collection and, in some instances, statistical treatment of material by members of the staff, particularly Janet Lipford, Margaret Johnston, and Margaret Anderson.

At Birth: Weight, length and a weight/length cubed index.
At One Month: Skeletal development (number of ossification centers present in the extremities on the left side).
At Three Months: Gain in weight, gain in length, and gain in skeletal development.
At Six Months: Gain in weight, gain in length, and gain in skeletal development.

Differences between infants, on the basis of the above characteristics, were analyzed as follows:

1. Infants of mothers with a low B.M.R. at ninth month of pregnancy were compared with infants of mothers with a high B.M.R. at ninth month of pregnancy.

2. Infants of mothers with a low B.M.R. *gain* during pregnancy were compared with infants of mothers with a high B.M.R. *gain* during pregnancy.

The intermediate groups were disregarded.

The following limits defined a low or a high classification in each category:

1. B.M.R. in Ninth Month of Pregnancy:
   Low—a B.M.R. of +1 and less (55 cases)
   High—a B.M.R. of +12 and more (43 cases)
2. Gain in B.M.R. During Pregnancy:
   Low—a gain of 8 and less (40 cases)
   High—a gain of 20 and more (43 cases)

In comparing the infants, boys and girls were at first treated separately and then grouped for final analysis, when it was determined that for the present study separate consideration of the sexes did not significantly change the results.

Results

Table I shows a comparison of infants of mothers with low ninth month B.M.R. and infants of mothers with high ninth month B.M.R.

TABLE I. A COMPARISON OF MEAN VALUES FOR VARIOUS PHYSICAL ITEMS. "LOW B.M.R. GROUP" CONTAINS INFANTS OF MOTHERS WITH LOW B.M.R. IN THE NINTH MONTH OF PREGNANCY; "HIGH B.M.R. GROUP" CONTAINS INFANTS OF MOTHERS WITH HIGH B.M.R. AT THIS PERIOD

	WEIGHT (GM.)			HEIGHT (CM.)			OSSIFICATION (NO. CENTERS)			WT. L^3
	BIRTH	GAIN		BIRTH	GAIN		1 MO.	GAIN		BIRTH
		3 MO.	6 MO.		3 MO.	6 MO.		3 MO.	6 MO.	
Low B.M.R. group	3,374	2,341	4,120	50.1	9.9	16.3	4.1	2.6	5.9	271
High B.M.R. group	3,588	2,314	4,067	50.8	10.1	16.1	4.4	2.5	5.4	272
Difference	214	27	53	0.7	0.2	0.2	0.3	0.1	0.5	1
Critical ratio of difference	2.3	--	--	1.3	--	--	--	--	1.7	--
Group leading	High	Low	Low	High	High	Low	High	Low	Low	High

Infants of mothers with high B.M.R. were heavier and longer at birth and more advanced skeletally at one month than infants of mothers with low B.M.R. This difference is statistically significant in the case

of birth weight. Infants of mothers in the low group tended to gain faster in weight, height and ossification during the first six months than did the infants in the high group. There is only a slight difference between the children in the weight/length cubed index at birth, the infants of the high group weighing slightly *more* per unit length.

Table II shows a comparison of children of mothers with a low B.M.R. *gain* during pregnancy and children of mothers with a high B.M.R. gain during pregnancy.

TABLE II. A COMPARISON OF MEAN VALUES FOR VARIOUS PHYSICAL ITEMS. "LOW B.M.R. GAIN GROUP" CONTAINS INFANTS OF MOTHERS WITH LOW GAIN IN B.M.R. DURING PREGNANCY. "HIGH B.M.R. GAIN GROUP" CONTAINS INFANTS OF MOTHERS WITH HIGH GAIN IN B.M.R. DURING THIS PERIOD

	WEIGHT (GM.)			HEIGHT (CM.)			OSSIFICATION (NO. CENTERS)			WT. L^3
	BIRTH	GAIN 3 MO.	GAIN 6 MO.	BIRTH	GAIN 3 MO.	GAIN 6 MO.	1 MO.	GAIN 3 MO.	GAIN 6 MO.	BIRTH
Low B.M.R. gain group	3,268	2,336	4,205	49.6	10.1	16.7	4.1	2.6	5.6	268
High B.M.R. gain group	3,584	2,254	4,099	50.9	9.9	16.2	4.8	2.8	5.9	274
Difference	316	82	106	1.3	0.2	0.5	0.7	0.2	0.3	6
Critical ratio of difference	3.0	--	--	2.7	--	1.3	1.7	--	--	1.0
Group leading	High	Low	Low	High	Low	Low	High	High	High	High

Infants of mothers with a high B.M.R. gain were heavier and longer at birth and more advanced skeletally at one month than infants of mothers in the low gain group. These differences are statistically significant in the case of birth weight and birth length. Infants of mothers in the low gain group during pregnancy gain faster in weight and length during the first six months. Rate of gain in ossification in the two groups is almost the same, favoring slightly the high group. The high group has a slightly larger weight/length cubed index, that is, they were heavier per unit length.

TABLE III. A COMPARISON OF MEAN VALUES FOR VARIOUS PHYSICAL ITEMS. "LOW B.M.R.—LOW GAIN GROUP" CONTAINS INFANTS OF MOTHERS WITH BOTH LOW B.M.R. IN THE NINTH MONTH OF PREGNANCY AND LOW GAIN IN B.M.R. DURING PREGNANCY; "HIGH B.M.R.—HIGH GAIN GROUP" CONTAINS INFANTS OF MOTHERS IN THE OPPOSITE CATEGORY

	WEIGHT (GM.)			HEIGHT (CM.)			OSSIFICATION (NO. CENTERS)			WT. L^3
	BIRTH	GAIN 3 MO.	GAIN 6 MO.	BIRTH	GAIN 3 MO.	GAIN 6 MO.	1 MO.	GAIN 3 MO.	GAIN 6 MO.	BIRTH
Low B.M.R.—Low gain group	3,321	2,548	4,389	49.6	10.2	16.7	3.9	2.4	5.6	271
High B.M.R.—High gain group	3,682	2,401	4,197	51.3	10.0	16.2	4.6	2.6	5.3	273
Difference	361	147	192	1.7	0.2	0.5	0.7	0.2	0.3	2
Critical ratio of difference	2.8	--	--	2.6	--	--	1.7	--	--	--
Group leading	High	Low	Low	High	Low	Low	High	High	Low	High

An examination of our data indicates that the mothers who show a low B.M.R. at ninth month are also in many cases mothers with a low B.M.R. *gain* in pregnancy. The coefficient of correlation (r) between ninth month B.M.R. and the B.M.R. gain is +0.68. It was therefore felt that a selection of infants based on still another low-high comparison might prove interesting. In Table III, the infants of mothers who have both a low B.M.R. in the last month of pregnancy and a low B.M.R. gain during pregnancy are compared to infants who are high in both categories.

This comparison sharpens the differences already presented. The high group is advanced at birth, and heavier per unit length, while the low group tends to gain faster during the first six months. These differences are statistically significant for birth weight and birth length.

Discussion

Arnold,[1] in a preliminary report, suggests with caution that he has "reduced fetal obesity" by feeding pregnant women 3 to 6 grains daily of desiccated thyroid gland throughout gestation. The infants of 116 mothers so treated had a mean weight of 6.8 pounds. While Arnold has no control group for his thyroid treated mothers, it is presumed that the average weight of 6.8 pounds is below that which would be expected in an untreated series. It is, perhaps, unfortunate that he has no length measurements on his infants. If he had, it is possible that he would have found his infants smaller in length as well as weight. If so, we believe it may be assumed that by giving 3 to 6 grains of desiccated thyroid per day to his mothers, he was then dealing with a group with higher than average B.M.R. The comparison of basal rates in our group with the height, weight and other factors of the children is at first glance contradictory to Arnold's findings and conclusions. Perhaps it is justifiable, therefore, to devote a bit of space to a discussion of possible causes for the discrepancy in our observations.

In considering what effect the feeding of thyroid during pregnancy might have upon the weight of the newborn infant, it is well to think for a moment about the results of hypo- and hyperthyroidism in young animals. Kennedy[2] states, "The results of feeding large amounts of thyroid substance to young animals are manifested chiefly in a diminished rate of growth, hypertrophy of such organs as the suprarenals, heart, liver, pancreas, spleen, testes, ovaries, and in diminished weight. Cessation of feeding of thyroid gland is followed by acceleration in the rate of growth and in disappearance or hypertrophy of the organs." The same author, in discussing thyroidectomy in young animals, says, "In general there is a retardation of growth, evident particularly in the skeleton, and a depression of all physiological functions of the body." It should be evident then that in the young we are dealing with a thyroid effect which is absent in the adult, namely the control of growth. Effect of thyroid upon the weight of an adult may be primarily on the excess storage of fat. Effect of thyroid upon the weight

of a young child or fetus may be primarily upon the infant's total growth, not its formation of adipose store. Arnold in "reducing fetal obesity" by feeding mothers thyroid may very well simply be depressing the growth of the child, just as the growth of any child suffering from hyperthyroidism is depressed. The real nature of this weight reduction would be shown if Arnold had considered birth lengths.

Arnold's basis for using thyroid therapy as a general procedure in pregnancy is that he believes a state of hypothyroidism normally exists during pregnancy. He draws this conclusion despite the commonly accepted finding of a high basal metabolic rate during late pregnancy. His conclusion is based on the fact that he fails to produce signs and symptoms of hyperthyroidism in his pregnant mothers when he administers 3 to 6 gr. of desiccated thyroid per day. Let us consider for a moment the basis for Arnold's interpretation of thyroid activity during pregnancy. It is a well-established fact that there is normally a rise of perhaps 15 per cent in mothers' B.M.R. as term approaches. Rise in B.M.R. in the absence of infection is in general considered evidence of increased thyroid activity. The rise in pregnancy has been attributed by various investigators both to an increase in the thyroid activity of the mother and to the increasing function of the thyroid of the fetus. Palmer,[3] et al., and many others have indicated that the fetal thyroid becomes active at a very early stage, and that the fetus undoubtedly supplies most or all of its own thyroid needs; and perhaps upon occasion, some of those of the mother. The increased oxygen consumption in pregnancy, then, while resulting from either increased maternal thyroid activity or from fetal thyroid, probably represents a higher rate of oxygen consumption by the maternal tissues, as well as by the fetal tissues.

Bodansky and Duff[4] and others, working with animals, have found that there is a much greater tolerance of thyroxin during pregnancy than in a nonpregnant state. Now a large tolerance of thyroid hormone in the nonpregnant state may or may not be considered adequate evidence of the existence of hypothyroidism. Certainly it is highly doubtful whether such a tolerance during pregnancy should be so interpreted. It must be remembered that the altered physiologic state of pregnancy involves many functions, including possibly the development of antihormones, and inhibitory actions by other endocrines. Furthermore, unless we are to change our concept of the terms normal and hypo function, "normal thyroid function" during pregnancy must mean to us the thyroid function usually or customarily existing during that state. Hypothyroid function during pregnancy should mean a degree of function distinctly below that *usually existing during pregnancy*. We must be aware also of the possibility of a selective action of excess thyroid hormone on the mother and fetus. Perhaps the mother herself, through antihormone action or other means maintains a broad tolerance for excessive thyroid substance during pregnancy. Does her fetus, how-

ever, develop a similar tolerance or resistance to excess thyroid? Is it not possible that large doses of thyroid may be well tolerated by the mother but that the high blood levels of thyroid hormone such treatment involves might induce in the fetus a state of hyperthyroidism sufficient to depress growth?

How then may we reconcile our findings that mothers with the higher ninth month rates and with the larger B.M.R. gains, have the largest children, with Arnold's findings that feeding large amounts of desiccated thyroid to normal women produces lighter infants. It seems logical that within the *normal range* of thyroid function, a more adequate, a more optimum level of the hormone would exercise its usual physiologic function of promoting growth—in this instance fetal growth. Since we are in the goiter belt, it is reasonable to believe that some of our mothers do not have entirely optimum thyroid function (and perhaps the same conclusion applies to the fetus). Fetuses of such women would not, therefore, be able to exploit their full intrauterine growth potentialities, and would be somewhat smaller than those of mothers with entirely adequate thyroid function. That such is the case is suggested by the results of our study as shown in Tables I, II, and III. The infants of the mothers with lower basals are smaller than those with higher basals. But in addition, the infants of mothers with the lower basals *are actually less obese* as shown by their weight-length relationships, than are those of mothers with higher basals. This fact is important. It may be argued that mothers with larger babies might be expected to have higher basal rates, because of the higher proportionate weight of high oxygen consuming fetal tissue. Such an explanation still would not account for the lower weight-height relationship of the infants of the low B.M.R. group.

One may wonder whether a similar relationship exists between the thyroids of a mother and fetus as exists between pancreas of mother and fetus. It is known that in maternal diabetes, the fetal pancreas hypertrophies and produces a great deal more insulin than normally in an attempt to compensate for the nonfunctioning maternal pancreas. The result is that although this process is never successful in maintaining fetal blood sugar at its normal level, because of the dilution effect of attempting to supply the whole maternal fetal economy with insulin, the fetus as a newborn has an overactive pancreas. If similarly the fetal thyroid developed an abnormally high rate of activity as a result of maternal deficiency, it might or might not be able to supply both organisms adequately, but it might be an overfunctioning gland at birth. Depending upon how soon its function returned to normal levels, this overactive state might retard early neonatal growth, stimulate that growth, or have little effect. Growth rates of infants of the high and low mothers' basal groups are not greatly different. The infants of the low mothers' basal group do, however, in general have slightly more

rapid growth progress than those of the high group in weight, ossification and height.

Summary

The infants of a "normal" group of mothers were divided into two groups according to the basal metabolic rates of the mothers during the ninth month of pregnancy. A similar division was made on the basis of the mothers' B.M.R. gain during pregnancy. In each instance the infants of the high B.M.R. group were compared with the low B.M.R. group in terms of birth weight and length, weight/length cubed index, and number of ossification centers present in the extremities of the left side (at one month), together with the gains in these categories during the first six months of life. Infants of mothers in the high ninth month B.M.R. group were larger and skeletally slightly more mature than infants in the low B.M.R. group. So were infants of mothers with high B.M.R. gains during pregnancy. Infants in both high groups weighed slightly *more* in relation to their lengths, than did the infants of the low groups. There was some tendency for the infants of the low groups to gain slightly more rapidly in weight, height and ossification during the first six months of life.

Conclusions

There is no evidence from our data that higher basal metabolic rates of mothers during pregnancy are effective in producing smaller or less "obese" babies so long as a state of actual hyperthyroidism does not exist. We question the use of thyroid therapy in normal women for the production of less "obese" infants, since we believe that smaller infants are produced by such means only if the therapy is severe enough to depress all fetal growth processes through the creation of a state of actual hyperthyroidism.

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EXPERIMENTAL BASIS FOR THE CHEMOTHERAPY OF TRICHOMONAS VAGINALIS INFESTATIONS. II*

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LABORATORY evaluation of the in vitro killing and inhibiting effect of various chemicals on *Trichomonas vaginalis* offers useful collateral data for clinical studies and suggests new preparations worthy of therapeutic trial. Several investigators have recorded their observations of the ability of various compounds to kill *T. vaginalis*.[1-13] Differences in technique make comparison of the recorded data difficult. In addition all recorded tests have presumably been made with bacterially contaminated trichomonads. The detrimental effect of bacterial growth on *T. vaginalis* is well known.

Method

A standardized technique for testing the protozoacidal action of chemicals employing bacteria-free *T. vaginalis*[15-16] has been recorded.[14] In summary it consists of introducing a standard number of bacteria-free *T. vaginalis* (400,000) into a standard volume (4 c.c.) of a drug solution containing 25 per cent human serum adjusted to pH 6 with N/1 HCl. A constant temperature of 37° C. is maintained. Subcultures of 2,000 protozoa are removed at intervals of 5 and 10 minutes by pipette and introduced into C.P.L.M.† medium[14] which will initiate growth if as many as ten or even less viable protozoa capable of multiplying are present. Sterile technique is employed throughout.

The effective concentration of the compound in question is arbitrarily given as that which kills in 10 but not in 5 minutes. Failure to multiply in the C.P.L.M. medium is taken as an indication that the protozoa were killed by contact with the medicament. When all the tested compounds are compared in this manner a relative evaluation of their lethal effect is obtained.

Acidified human serum is employed in the test mixture to simulate empirically the high protein and acid content of vaginal discharge which a successful in vivo trichomonacide must overcome.

The chemicals tested include a large number solicited from various commercial sources, whose cooperation in this study is much appreciated. No compound submitted has been omitted from these experiments. In addition, many other chemicals have been tested for reasons of theory or previous clinical trial. A restricted program for the future makes provision for testing the action of many other compounds as well as their growth-inhibiting action. Interested individuals should feel free to submit material for testing to the junior author.

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†C.P.L.M. = cystine, peptone, liver infusion, maltose.

TABLE I. PART A. TRICHOMONACIDAL COMPOUNDS

Summary of experiments testing the killing action of various chemicals on bacteria-free *Trichomonas vaginalis*. All tests were made in 25 per cent acidified human serum against a standard number of organisms (400,000) in a standard volume (4 c.c.)

COMPOUND TESTED	CONCENTRATION KILLING IN 10 BUT NOT IN 5 MIN.	pH OF TEST MIXTURE
Acetic anhydride	1:400	3.92
Acetarson (Stovarsol)	1:20	8.99
Acriflavine hydrochloride	1:5,200	
Acriflavine-neutral	1:5,000	
Aerosol	1:500	5.27
Aldarsone	1:140-1:150	6.20
Ammonium thiocyanate	1:250-1:300	6.03
Aniline	1:[illegible]0-1:125	6.72
Arsphenamine	1:3,100-1:3,400	5.3-5.8
Benzoic acid	1:600	4.4
Boric acid	1:28 (in 90 min.)	5.6
Butyl alcohol	1:40	6.3
Butyric acid	1:250-1:260	3.94
Cadmium chloride	1:900	5.58
Caprylic acid	1:900-1:1,000	5.0
Caprylic alcohol	1:500-1:600	5.99
Chloroform	1:300-1:400*	6.02
Chromium trioxide	1:1,000-1:1,100	4.33
Citric acid	1:60	2.29
Colloidal chlorothymol	1:2,200	6.28
Cresol-compound solution	1:400-1:500	6.66
Cresylic acid	1:500	6.11
Cupric sulfate	1:1,100	4.9
Dihexylin, aqueous	1:5,800	3.64
Dihexylin, tincture	1:5,500-1:6,000	5.00
Emetine hydrochloride	1:36	5.7
Ethyl alcohol	9.5-14.25%	6.32
Ethylhydrocupreine hydrochloride	1:142 (in 45 min.)	4.82
Ethyl mercuric chloride	1:42,000	6.3
Floraquin	70% saturated (in 30 min.)	5.4-5.8
Formaldehyde	1:400	6.16
Formic acid	1:500	4.12
Fumaric acid	1:300-1:400	3.37-3.9
Gentian violet	1:1,400-1:1,500	6.2
Glycerin	25%-30%	6.8
Green soap	1:400-1:450	7.14
Hexylresorcinol	Excess in emulsion	6.01
Hydrobromic acid	1:250-1:300	2.22-2.68
Hydriodic acid	1:400-1:450	3.43
Isomamyl hydrocupreine hydrochloride	1:250	5.3
Lactic acid	1:212-1:255	3.4-3.5
Lead acetate	1:100	5.8
Levulinic acid	1:150-1:175	3.88
Malachite green	1:2,000	5.3
Maleic acid	1:250	3.02
Malonic acid	1:200-1:300	3.1-3.42
Mandelic acid	1:350	3.95
Mercuric bromide	1:15,000	6.4
Mercuric chloride	1:23,000	6.4
Mercuric oxycyanide	1:7,200-1:7,700	6.1
Mercurochrome	1:800	6.75
Merthiolate	1:13,000	6.7
Methyl alcohol	15%-20%	6.5
Methyl violet 6B	1:5,000	6.5
Monochloracetic acid	1:900	4.2
N^1-benzoylsulfanilamide	10% saturated	10.2
Negatan	1:120-1:140	1.76-2.09

*Approximate.

TABLE I—CONT'D

COMPOUND TESTED	CONCENTRATION KILLING IN 10 BUT NOT IN 5 MIN.	pH OF TEST MIXTURE
Neoarsphenamine	1:2,000	6.12
N^1-furfurylsulfanilamide	8% saturated	10.7
Oxalic acid	1:300-1:400	3.4-3.55
Oxyquinoline sulfate	1:150-1:175	4.30-4.37
Phemerol	1:1,600	5.98
Phenol	1:210	5.9-6.2
Phenyl mercury derivative of p-amino-benzene sulfanilamide	1:24,000-1:26,000	6.4
Phenylmercuric acetate	1:40,000	5.81
Phenylmercuric benzoate	1:36,000-1:38,000	5.8-6.0
Phenylmercuric chloride	1:34,000-1:38,000	5.8-6.0
Phenylmercuric nitrate	1:36,000-1:38,000	5.8
Phosphoric acid	1:200	1.98
Picric acid	1:400-1:500	4.5
Potassium chromate	1:100	7.37
Potassium dichromate	1:400	5.8
Proflavine	1:4,400-1:4,600	6.1
Propionic acid	1:200-1:250	3.96-4.02
Propylene glycol	20-25%	6.1
Pyrogallic acid	1:60-1:80	5.85
Pyroligneous acid	1:20-1:30	3.87-4.08
Quinine hydrochloride	1:100	6.3
Saponin	1:200	6.27
Salicylic acid	2.1-1.1 saturated solution	
Saponified castor oil	1:600	6.85
Selenium oxide	1:350-1:400	3.02-3.18
Silver nitrate	1:28,000-1:30,000	6.3
Silver picrate	1:14,000-1:17,000	6.08-6.13
Sodium carbonate	1:100-1:120	9.97
Sod. cobalti nitrite	1:400-1:500	5.02-5.19
Sod. nitroferric cyanide	1:250-1:300	6.0
Strong silver protein	1:1,300-1:1,400	6.2
Succinic acid	1:140	3.57
Sulfanilylacetamidine	1:400	10.05
Sulfanilamidothymol	1:250	10.29
Sulfarsphenamine	1:3,000-1:4,000	6.0-6.2
Sulfosalicylic acid	1:150-1:200	2.27-2.72
Superoxyl	1:60-1:80	5.0
Tartar emetic	1:1,600-1:2,000	5.63-6.0
Tartaric acid	1:60-1:80	2.33-2.46
Thiobismol	1:200-1:300	6.9-7.32
Trichloracetic acid	1:400	3.2
Triethanolamine	1:20	9.78
Tryparsamide	1:175	6.30
Uranium acetate	1:200*	4.66
Valeric acid	1:250-1:300	4.1
Vioform	70% saturated or 10% Emulsion	6.3
Vuzin dihydrochloride	1:2,000	5.81
Zinc acetate	1:140 (in 45 min.)	5.22

Results

The data obtained to the present are tabulated as follows: Table I lists those compounds which exhibit trichomonacidal activity and Table II includes those which failed to kill *T. vaginalis* in vitro within 10 minutes under the experimental conditions employed. Table III summarizes the work done on jellies.

TABLE II. INACTIVE COMPOUNDS

Summary of experiments in which the compounds tested did not kill the standard dose of *T. vaginalis* in ten minutes in the highest concentration tested.

In exploration of many nonproprietary compounds, it was considered impractical to test solutions of higher concentrations than 1:100, since the purpose of the study was to discover substances of greater activity than those now in use. The upper level of concentration was limited in other instances by: (a) the solubility of the compound in question, (b) the concentration of a stock solution as supplied by the manufacturer, (c) dilution resulting from the addition of serum.

COMPOUND TESTED	HIGHEST CONCENTRATION TESTED	pH OF TEST MIXTURE
Acetaldehyde	1:20	4.48
Acid fuchsin	1:133	4.8
Alizarin	3:1 saturated	6.58
Alloxan	1:100	3.5
Aluminum amm. sulfate	1:20	3.4
Aluminum chloride	1:100	3.44
Aluminum pot. sulfate	1:20	
p-amino dimethyl Aniline monohydrochloride	1:133	4.77
Ammonium acetate	1:20	5.99
Ammonium bromide	1:20	6.36
Ammonium chloride	1:20	6.18
Ammonium oxalate	1:100	
Aseptoform-p	3:1 saturated solution	6.26
Basic fuchsin	1:133	5.94
Biebrich scarlet	3:1 saturated	7.14
Brilliant cresyl blue	3:1 saturated	4.12
Carbarsone	1:100	7.79
Carbon tetrachloride	0.375%	6.4
Carbon bisulfide	0.075%	
Chiniofon	1:70	6.2
Cotton blue	1:133	5.96
Cresol red	3:1 saturated	6.04
Devegan	70% saturated	
Dichloramine T.	3:1 saturated	6.31
Diethylene glycol	1:20	6.73
Diphenylamine	3:1 saturated	
Eosin Y	1.5%	7.0
Ethyl ether	3.75%	6.67
Ferric amm. sulfate	1:400	4.21
Ferrous amm. sulfate	1:20	4.89
Formamide	1:20	6.46
Gallic acid	1:133	3.91
Glycerol phosphate	1:100	7.45
Hippuric acid	3:1 saturated	
Iodoform	70% saturated	6.5
Iso-amylic alcohol	1:100	
Janus green B	1:133	5.5
Lactose	11.25%	7.06
Lenigallol	10% suspension	5.1
Lithium carbonate	1:266	
Lithium lactate	1:133	
Manganous sulfate	1:100	
Magnesium sulfate	1:5	6.01
Malic acid	1:40	2.37
Metacine	6% suspension	3.11
Methyl orange	3:1 saturated	7.2
Methyl red	3:1 saturated	5.36
Methylene blue	1:40	
Naphthylamine	3:1 saturated	
Neutral red	3:1 saturated	5.03
Nigrosin	3:1 saturated	7.68
Oleic acid	0.75%	6.45
Phenol red	1:133	3.9

TABLE II—CONT'D

COMPOUND TESTED	HIGHEST CONCENTRATION TESTED	pH OF TEST MIXTURE
Phthalic acid	1:100	4.16
Picramic acid	3:1 saturated	6.16
Potassium acid phthalate	1:100	4.22
Potassium bromate	1:100	6.2
Potassium chlorate	1:133	6.53
Potassium ferricyanide	1:100	6.15
Potassium ferrocyanide	1:20	6.42
Potassium iodide	1:20	6.78
Potassium permanganate	1:100	8.34
Potassium persulfate	1:133	4.18
Propyl ester of parahydroxy benzoic acid	3:1 saturated	6.26
Pulvis alkalinus fungi	70% saturated	8.82
Quinine sulfate	1:1,000	5.43
Red mercuric iodide	3:1 saturated	6.6
Red mercuric oxide	3:1 saturated	6.68
Safranin	1:133	6.68
Sodium acetate	1:100	6.47
Sodium alizarin sulfonate	1:133	4.93
Sodium anthraquinonesulfonate	1:140	6.1
Sodium barbital	1:100	8.4
Sodium benzoate	1:100	6.31
Sodium bicarbonate	saturated	8.47
Sodium 2-5-bisulfanilamido-benzenesulfonate	1:1,000	5.6
Sodium borate	1:100	8.77
Sodium bromide	1:100	6.18
Sodium N^1-cinnamoyl-sulfanilamide	1:1,000	5.80
Sodium hyposulfite	1:100	5.5
Sodium molybdate	1:100	6.47
Sodium oxalate	1:100	6.78
Sodium pyrophosphate	1:100	8.0
Sodium sulfite	1:100	7.82
Sodium thiocyanate	1:100	6.3
Sodium thiosulfate	1:100	6.23
Sulfanilic acid	1:133	3.12
Sulfadiazine	1:14,000	
Sulfaguanidine	1:750	5.5-6.0
Sulfamethyldiazine	1:4,700	5.5
Sulfanilamide	1:178	5.8
Sulfapyridine	1:3,500	5.4
Sulfathiazole	1:1,100	5.57
Sulfathiazole and Beta lactose	70% saturated	5.69
Tannic acid	1:20	
Thymol	1:1,250	6.31
Toluol	1:200	6.14
Zephiran	1:1,400	6.2
Zinc acetate	1:100	5.7
Zinc chloride	1:133	5.3

Comments

1. Three to one saturated = 3 parts of a saturated (aqueous) solution and 1 part of 100 per cent serum.

2. Potassium permanganate in a concentration of more than 1 per cent forms a solid with the serum. The technique employed in these experiments does not give a fair evaluation of the trichomonacidal effect of the compound.

TABLE III. JELLIES. SECTION I

Water-dispersible jellies offer a suitable medium in which to determine trichomonacidal properties. A tragacanth-acacia jelly base* was used as a vehicle. The pH was varied; acetic acid was used for adjustment of acid jellies to pH above 3.0, citric acid for pH of 3.0 or below, and sodium hydroxide for alkaline levels. All dilutions were made with 25 per cent serum adjusted to pH 6. That pH, per se, of the undiluted jelly is not always effective in killing Trichomonas is shown in the following table.

	INACTIVE—DID NOT KILL TRICHOMONADS IN 10 MIN.									
JELLY NO.	163-1	163	126-A	151-3-B-3	163-1	122	2S24J	2S25J	126B	126C
Jelly pH	2.5	3.5	4.0	4.5	4.0	7.0	8.0	9.0	7.0	7.0
Jelly dilution	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10
pH test mixture	4.15	4.41	5.08	5.61	4.9	7.88	8.47	8.87	7.73	7.82

Also Inactive:
126B—(Above) plus Gentian violet 1%
126C—(Above) plus Iodine 1%, KI 2%

*Jelly base: Tragacanth 3%, acacia 2%, boric acid 3%, glycerin 5%, propylene ester of parahydroxy benzoic acid 0.05%, water to 100%.

TABLE III. SECTION II

Sulfonamides in a gum base, prepared as above, did not exhibit trichomonacidal properties at the pH levels selected, as illustrated in the following table.

	INACTIVE—DID NOT KILL TRICHOMONADS IN 10 MIN.												
	151-3-B-2	151-3-B-1	146B	146C	146D	146E	146A	151-1-A	151-1-B	151-1-D	151-1-E	151-2-D	151-2-E
Sulfathiazole %	5	5	10	15	20	30	5	–	–	–	–	–	–
Sulfanilamide %	5	5	–	–	–	–	–	5	15	20	30	20	30
pH	4.0	4.5	4.5	4.5	4.5	4.5	7.0	4.5	4.5	4.5	4.5	7.0	7.0
Dilution	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:10	1:40	1:40
pH test mixture	4.98	5.6	5.08	5.08	5.12	5.18	7.7	5.23	5.12	5.21	5.6	6.25	6.15

TABLE III. SECTION III

The trichomonacidal activity of chemicals is apparently influenced by the pH of the jelly. When ricinoleic acid (0.75%) and oxyquinoline sulfate (0.25%) are added to the base jelly used above, the effectiveness varies, with maximum trichomonaicidal activity obtained when the pH is maintained at acid levels.

	ACTIVE—DILUTION KILLING IN 10 MIN. BUT NOT IN 5 MIN.												INACTIVE—DID NOT KILL IN 10 MIN.			
JELLY NO.	115A	115B	115C	115D	115E	115F*	115G	115H	115J	115K	F301†	41D3‡	115L	115M	115P	115R
Jelly pH	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	4.5	4.5	7.0	7.5	8.5	9.0
Jelly		1:120		1:120	1:100		1:80	1:120	1:100		1:120			1:20	1:20	
Dilution	1:160	1:160	1:160		1:160		1:100		1:160		1:160	1:80	1:20	1:40	1:40	1:10
				1:160		1:120		1:160		1:160						
pH test mixture					5.5		5.7	5.9	5.9				7.84	8.26	8.66	
	5.1	5.1	5.5	5.1	5.7	5.7	5.9	6.1	6.3	6.4	5.7	5.5	7.20	7.88	8.42	8.83

*Known commercially as Ortho-Gynol.
†F301 above jelly plus 20% sulfathiazole.
‡41D3 above jelly plus 0.25% sodium lauryl sulfate.

3. Ferric Amm. sulfate forms a solid with serum in concentrations greater than 0.25 per cent and cannot be adequately tested.

4. Superoxyl decomposes before a test can be completed. This is not a true evaluation of its activity.

Conclusions

1. There are many chemicals which are active trichomonacides in vitro in the presence of acidified 25 per cent human serum.

2. Many of these are so much more active than some commonly employed therapeutic preparations that clinical evaluation of their in vivo effectiveness when incorporated in a suitable vehicle such as a jelly is warranted.

3. Those compounds which were found to kill *T. vaginalis* in a dilution of 1:1,000 or more by the technique employed include:

Acriflavine hydrochloride
Acriflavine neutral
Arsphenamine
Caprylic acid
Chromium trioxide
Cupric sulfate
Dihexylin
Ethylmercuric chloride
Gentian violet
Malachite green
Mercuric bromide
Mercuric chloride
Mercuric oxycyanide
Merthiolate
Methyl violet 6B
Neoarsphenamine
Phemerol
Phenyl mercury derivative of p-amino benzene sulfonamide
Phenylmercuric acetate
Phenylmercuric benzoate
Phenylmercuric chloride
Phenylmercuric nitrate
Proflavine
Silver nitrate
Silver picrate
Strong silver protein
Sulfarsphenamine
Tartar emetic
Vuzindihydrochloride

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SALMONELLA CHOLERAESUIS BACTEREMIA DURING PREGNANCY

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EVIDENCE at hand indicates that Salmonella infections in man are definitely more common than typhoid fever at the present time in the northeastern part of the United States. Typhoid fever is a well-known complication of pregnancy and during the last 40 years, a number of articles have been published on this subject. In contrast, Salmonella infection in pregnancy seems to be a very unusual occurrence. A search through the *Quarterly Cumulative Index Medicus* of the last 10 years failed to reveal a single reference, and the Editor of the *Journal* of the *American Medical Association* states that "we have found no reference, whatsoever, to Salmonella infections during pregnancy." It seems to be of interest, therefore, to report here the clinical, bacteriological, and serological findings in a case of *Salmonella choleraesuis bacteremia* in pregnancy.

Report of a Case

Mrs. E. B., aged 24, was admitted to this hospital on November 24, 1943 with a diagnosis of toxemia of pregnancy. The date of the last normal menstrual period was April 25, 1943; that of expected confinement, February 2, 1944. The prenatal period was uneventful until 2 weeks prior to admission when it was found that her blood pressure had risen to 180/120 mm. Hg and her urine showed 4+ albumin. No other symptoms of toxemia were present. Concern over her condition was warranted particularly since a 6 months' pregnancy was terminated in March, 1942 because of high blood pressure and albuminuria. No further observations were made on the blood pressure until the present pregnancy. Her past history was essentially negative except for measles in childhood.

The patient was a short, obese female of Italian birth. The positive findings on physical examination were uterine enlargement of approximately 7 months' pregnancy and edema of the abdominal wall and legs. Fetal heart sounds were not heard, but the patient insisted that she felt life. The blood pressure was 180/110 mm. Hg; the urine showed 4+ albumin, some hyaline casts being present. A diagnosis of recurring toxemia was made. The patient was placed on a salt-free diet and fluids.

Severe epigastric pain requiring morphine occurred over a period of several nights. It was felt that these attacks were not the result of toxemia and other causes were considered. Roentgen-ray examination of the gall bladder was negative. Her temperature and pulse remained normal. Five days after admission, she required treatment for nasal bleeding which originated in a small eroded vessel. Her fluid intake and

output were satisfactory. Following the use of veratrone, the blood pressure was reduced to approximately 150/100 mm. Hg.

Seven days after admission (December 1), the patient had a chill and the temperature rose to 101° F. Physical examination was essentially negative. On the following day a second chill occurred with a temperature rise to 102° F. At that time the patient complained of pain in the right costovertebral angle and stated that she no longer felt fetal movements. Sulfathiazole (7.5 grains every 4 hours) was given for two days. The temperature remained elevated for 3 more days, fluctuating between 98.5° F., and 103° F. The pulse rate varied between 84 and 94 per minute. The systolic blood pressure ranged between 130 and 150 mm. Hg and the diastolic between 80 and 90 mm. Hg. On December 5, the blood culture, taken on December 3, was reported to be positive for paratyphoid bacillus and, consequently, the patient was transferred to the building for contagious diseases. On December 6 and 7, the temperature was normal. However, on December 8, the temperature rose to 102° F. and remained elevated until December 15, ranging between 100° F. and 103.6° F. On December 10, the patient went into spontaneous labor and was delivered of a macerated female fetus. On the first day post partum, the patient had another chill and the temperature rose to 103.6° F. Except for a slight rise of temperature to 100.2° F. on the third day post partum, the temperature remained normal until her discharge on December 20, the twenty-sixth day of hospitalization.

Results of Laboratory Investigations

The pertinent laboratory findings were as follows: During the entire period of hospitalization the urine of the patient contained albumin. Sugar was not present. A few red and white blood cells were seen in the majority of specimens. Occasionally, hyaline and granular casts were present.

A blood count taken on December 4, showed the following: 11 grams of hemoglobin; 3,100,000 red blood cells; 7,800 white blood cells; 67 per cent polymorphonuclear cells, 12 per cent band forms, 18 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles. On December 17, the hemoglobin was 8.5 grams and the leucocyte count 6,000. On December 20, the hemoglobin was 9.5 grams. The patient's blood was Rh positive.

Since the cause of the fever remained undetermined, a blood culture was taken on December 3. It revealed the presence of gram-negative bacilli, subsequently identified as *S. choleraesuis*. This organism is also referred to in the literature as *S. suipestifer*. On December 9, another blood culture was taken and again paratyphoid bacilli were recovered; there were 3 colonies per cubic centimeter of blood. The blood culture obtained on December 7, remained sterile.

In order to determine the possible portal of entry, a throat culture was taken on December 8, and the feces were cultured on December 9. Both cultures failed to reveal the presence of paratyphoid bacilli. It is interesting to note that stool specimens taken on December 9, 10, 13, and 15 likewise did not contain *Salmonella choleraesuis*. However, a stool specimen obtained on December 17 (18 days after the onset of the fever) showed paratyphoid bacilli on culture. On the same day the urine was positive for *S. choleraesuis*.

The antibody response of the patient was investigated and the following results were obtained. Blood serum was examined for the presence of agglutinins against stock strains of typhoid and paratyphoid bacilli, *B. proteus* OX_{19} and *B. abortus*. In addition, the strain isolated from the blood of the patient was used as antigen. The serum of the patient obtained on December 9, failed to agglutinate any of these organisms even when used in a dilution of 1:10. Two days later agglutinins against paratyphoid bacillus appeared. The titer against the stock strain of *B. paratyphosus* and the homologous strain was 1:320 and 1:640, respectively. Twenty-four hours later, December 12, the agglutinin titer against the patient's own strain was 1:2,560. It is evident, therefore, that the patient developed specific antibodies in high titer against *S. choleraesuis*. In this connection it may be pointed out that some authors, for instance, Wing and Tropoli,[1] interpreted the presence of antibodies in titer of 1:80 as indicative of antibody formation. Such a conclusion is not warranted unless it can be shown that the antibody titer increased during or following the infection and is definitely beyond the titer of normal agglutinins.

As previously mentioned, a macerated fetus was delivered on December 10, 1943. It should be noted that at that time the patient's temperature reached 103.6° F., and that, on the day before, the blood culture was positive for *S. choleraesuis*. Bacteriologic studies were carried out on both the fetus and the placenta in order to determine whether or not intrauterine transmission of the paratyphoid bacilli had taken place. The following are the results obtained: The culture taken from the aseptically opened placenta revealed the presence of numerous gram-negative bacilli, subsequently identified as *S. choleraesuis*. Cultures of the heart's blood and mouth of the fetus remained entirely sterile. Thus, it is obvious that, although the organisms were present in the placenta, they had not invaded the blood stream of the fetus.

The placenta was examined by Dr. Kornel L. Terplan who reported these findings:

The placenta measured 13.5 cm. in diameter and 1 to 3 cm. in thickness. There were numerous anemic infarcts. Histologically, considerable autolytic changes with marked leucocytic infiltration of autolytic and necrobiotic areas and with autolysis of the exudate itself were noted. In the areas in which the placental structure was well preserved, these exudative changes were not seen. A few white infarcts with minimal inflammatory changes were present. Some other sections showed calcification in the cotyledons and a few areas with peculiar leucocytic infiltration of partly disintegrating villi. In some areas the picture was almost phlegmonous, the near-by villi showed different degrees of necrobiosis. The umbilical cord was not remarkable.

The strains isolated from blood, stool, and urine of the patient and from the placenta were identical. The organism was a motile, gram-negative bacillus which grew well on artificial media. It produced acid and gas from glucose, maltose, mannitol, dulcitol, xylose, rhamnose, and sorbitol, but not from lactose, sucrose, and salicin. Indole was not formed. The strain was studied further by Dr. Erich Seligmann, New York Salmonella Center, who identified it as *S. choleraesuis*.

When gram-negative bacilli were first recovered from the blood of the patient, an attempt was made to identify the strain by serologic methods. To this end, the supernatant fluid of the broth culture was

mixed with diagnostic horse sera. Polyvalent antimeningococcus serum caused strong precipitation, whereas anti-*H. influenzae* serum and normal horse serum did not. Antimeningococcus serum reacted in dilutions up to 1:100. Since it is well known that horse sera are more apt to give nonspecific reactions, precipitation tests were also set up with rabbit sera. Antimeningococcus types 1 and 4 sera produced a strong reaction with the supernatant of the culture. Whether this reaction is due to normal antibodies in these sera, or due to common antigenic components in *S. choleraesuis* and meningococci cannot be stated with certainty. The observation, however, clearly shows that the results of serologic methods used in the identification of microorganisms should always be considered together with morphological, cultural, and biochemical data, if erroneous conclusions are to be avoided.

Discussion

The exact incidence of Salmonella infections in the United States, particularly with respect to the distribution of the various types, remains undetermined. In part, this is due to the fact that many cases are not suspected clinically and others are not proved bacteriologically or serologically. Salmonella infections are not reportable in all states, while in others, as for instance in the State of New York, only cases of clinical paratyphoid fever, namely those caused by paratyphoid A and paratyphoid B (*Schottmueller*) bacilli, are reportable. It is important to emphasize that various members of the genus Salmonella cause a variety of clinical syndromes, among others, paratyphoid fever, gastroenteritis, bacteremia and septicemia, endocarditis, meningitis, and other purulent infections.

A search through the available literature failed to reveal any reports on Salmonella infections during pregnancy. On the other hand, paratyphoid bacilli have been encountered in septic abortion and puerperal sepsis as, for instance, in cases due to *S. choleraesuis* reported by Bornstein, Saphra, and Strauss[2] and by Roth.[3] Noteworthy also is the fact that *S. choleraesuis* has been recovered as causative agent of salpingitis and parametritis (*Seligmann, Saphra, and Wassermann*[4]). Our case of *S. choleraesuis bacteremia* in pregnancy presents several interesting features. It should be emphasized that the correct diagnosis was made only by means of a routine blood culture. The strain was identified by the New York Salmonella Center. It seems reasonable to suggest that laboratories not equipped for the determination of the many types comprising the genus Salmonella should send subcultures to Salmonella Centers, such as the New York Salmonella Center under the direction of Dr. Erich Seligmann, or the Salmonella Center at Lexington, Kentucky under Dr. P. R. Edwards.

The fact that the patient developed specific antibodies in high titer during the course of the illness is additional proof of the pathogenic significance of *S. choleraesuis*. The agglutinin titer rose from less than 1:10 to 1:2,560.

Twelve days after the onset of the fever, stool and urine of the patient became positive for paratyphoid bacillus. It is not difficult to visualize the possible consequences that may result from the presence in a maternity hospital of a patient excreting *S. choleraesuis,* particularly, when one takes into consideration the fact that newborns and infants appear to be quite susceptible to Salmonella infections. For this reason, the patient was transferred to the department of contagious diseases as soon as the bacteriologic diagnosis of Salmonella infection was established.

The question arose as to whether or not intrauterine transmission of the paratyphoid bacilli had occurred. It is well known that typhoid bacilli may pass through the placenta. Diddle and Stephens[5] recently reported a case of typhoid fever in a newborn infant whose mother was convalescent from the disease. These authors collected reports of 78 cases of typhoid fever during pregnancy from the literature. In 18 cases the data were incomplete and the diagnosis may well have been erroneous. In the remaining 60 acceptable cases, 31 developed the disease during the last trimester of pregnancy and were delivered of living infants. However, only 17 of these babies survived longer than 4 days.

In the case here reported, *S. choleraesuis* was present in the blood of the mother and in the placenta. The evidence at hand indicates that this organism did not invade the blood stream of the fetus. It may be assumed, therefore, that the death of the fetus was not due to infection per se. On the other hand, it is possible, although by no means certain, that the bacteremia of the mother was a contributing factor to the fatal outcome; in all likelihood, it was not the result of the toxemia.

Summary and Conclusions

A case of *S. choleraesuis* bacteremia during pregnancy is presented, apparently the first to be reported in detail in the American literature in recent years. The febrile illness began in the seventh month of pregnancy, 12 days prior to delivery of a macerated fetus. The patient excreted paratyphoid bacilli in feces and urine 11 days after the onset of the infection. On the twelfth day of the illness, specific agglutinins appeared in high titer. The placenta contained paratyphoid bacilli, but cultures of the blood and mouth of the fetus remained sterile. The patient recovered from the paratyphoid bacillus infection. Various aspects of Salmonella infections are discussed.

The authors wish to express their sincere appreciation for the identification of the strain to Dr. Erich Seligmann, New York Salmonella Center, and to Dr. Kornel L. Terplan for the histologic report on the placenta.

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THE CONTROL OF MENORRHAGIA BY PROLACTIN*

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OF ALL the dysfunctions that are associated with the menstrual cycle of women and which are of discomfort and even hazardous to the health of the patient, menorrhagia presents the most formidable problem to the clinician. Inasmuch as the physiology of uterine bleeding is not entirely understood, it is quite apparent that the physiological concept of malfunction of the menstrual cycle is likewise confused and misinterpreted. In addition, failure to reproduce the phenomena of excessive uterine bleeding in the common laboratory animal has prevented adequate experimental investigation of this problem, and has led to empirical therapeutic procedures or radical surgical cures. Although many different forms of therapy have been suggested, none has assumed the position of a panacea for the control of excessive uterine bleeding. In view of the multitude of methods proposed for the alleviation of functional and pathological uterine bleeding, it is apparent that not one has been uniformly accepted as the ideal mode of therapy.

In a search for a satisfactory therapeutic tool to dam successfully the menorrhagic flow, we decided to investigate the possibilities of the lactogenic hormone, prolactin, since it was shown by Greenblatt et al[1-4] that blood from lactating women was a useful, though inconvenient mode of therapy in metropathic menorrhagia. Their rationale for employing this mode of therapy was based upon two lines of thought:

1. The only true period of physiologic amenorrhea other than pregnancy occurs during the interval of lactation.
2. Experimental evidence at that time had demonstrated the antigonadal effect of lactogenic preparations.

In view of the successful results obtained by adhering to such a therapeutic regimen and the recent demonstration of the luteotrophin action of lactogenic preparations, impetus was attained to investigate further the problem of menorrhagia, employing commercial preparations of lactogenic hormone as the therapeutic measure. The effectiveness of the blood of lactating women in suppressing excessive uterine bleeding, as described in earlier reports, might well be ascribed to the presence of lactogenic hormone in the blood stream at this time.[5-6]

While this work was in progress, Hall[7] reported on the efficacy of lactogenic preparations in controlling excessive uterine bleeding. In presenting the results of this investigation, we substantiate the findings

*This study was supported in part by a grant from Armour Laboratories, Chicago, Ill., to the Department of Experimental Medicine administered by Robert B. Greenblatt.

of earlier work[1-4] and those of Hall and also present some preliminary data on the effect of prolactin upon the normal menstrual cycle and threatened abortion.

Procedure

Two types of purified prolactin preparations were employed in this investigation.* One type of preparation was available as a sterile powder and supplied with a solvent (saline or distilled water) to be added before using, while the other preparation was made up in solution form. We have found the powdered preparations to be more effective in treatment and saline to be the preferred solvent. The lactogenic hormone was administered for various periods of time to 43 women exhibiting organic or functional uterine bleeding. In patients suffering from organic disturbances such as fibromyoma, pelvic inflammatory disease, etc., it is to be emphasized that the lactogenic medication was purely palliative in action and was not employed with the intention of alleviating the organic disturbance. By controlling the excessive uterine bleeding in these patients, a suitable interval was provided between the cessation of bleeding and preparation of the patient for a more final and complete cure.

The doses of prolactin that were employed ranged from 100 to 250 International Units per injection and were administered subcutaneously every day, or second day during the abnormal period of bleeding. In several cases where the menorrhagia had been of long duration, it was necessary to administer 100 to 200 I.U. of prolactin in daily doses for 4 to 8 days before the bleeding could be checked. When possible, suction curettages were undertaken to determine the condition of the endometrium before and during administration of prolactin. Uterine biopsies were taken for a twofold purpose:

1. To determine the type of endometrium from which bleeding occurred.
2. To ascertain activity of the ovary by noting its physiologic effect upon the endometrium.

Operative specimens of the uterus or ovaries, or both, were also obtained and studied, particularly in patients undergoing hysterectomy, for additional evidence on the physiologic action of prolactin.

In addition to the patients exhibiting abnormal bleeding, three women with normal cycles were treated with daily doses of prolactin to determine the effect of the lactogenic hormone upon the length of cycle and endometrial histology.

Preliminary data are also presented on the effect of prolactin in six cases of threatened abortion. Four patients gave a history of previous abortion, while two presented a history of earlier uncomplicated pregnancies. These patients were all subjected to an intensive course of prolactin therapy in an attempt to control the untoward symptoms which were associated with cramps and bleeding.

Results

The data summarizing the results obtained with prolactin are presented in Table I, where the clinical outcome is classified as follows:

(a) Excellent—indicating prompt and complete control of the uterine bleeding.

*Prolactin preparations were generously supplied by Armour Laboratories, E. R. Squibb and Sons, and Winthrop Chemical Co.

(b) Good—referring to those cases where longer therapy was necessary to control bleeding.
(c) Fair—those cases in which bleeding was largely suppressed, but never completely inhibited, so that the patient exhibited a prolonged but mild menstrual flow during the administration of prolactin.
(d) Poor—indicating no diminution of bleeding following lactogenic treatment.

TABLE I. CLINICAL EFFECTS OF PROLACTIN

CHIEF COMPLAINT	ASSOCIATED WITH	CLINICAL RESULTS (NUMBER OF CASES)			
		EXCELLENT	GOOD	FAIR	POOR
Menorrhagia	Functional bleeding	8	7	1	1
Menorrhagia	Uterine fibromyoma	8	12	1	2
Menorrhagia	Cystic ovaries	3	3	2	1
Menorrhagia	Chronic pelvic inflammatory disease	5	4	3	2
Dysmenorrhea	Menorrhagia	5	3	4	2
Threatened abortion	Cramps and bleeding	3	0	0	3

In the accompanying chart, menorrhagia is listed as being associated with other clinical symptoms or entities such as fibromyoma of the uterus, cystic ovaries, chronic pelvic inflammatory disease, etc. In presenting the summary in a chart form, some cases have been itemized in more than one group due to dual complaints. For example, a patient with fibromyoma might also be subject to dysmenorrhea at onset of the menses which, in turn, might be menorrhagic in nature. Likewise, cystic ovaries or fibromyoma might be present in a menorrhagic patient. The clinical results are evaluated on the basis of the chief complaint and not upon the improvement of the associated conditions. Hence, although 43 patients in all were treated for abnormal bleeding, a great many more notations are included in the chart due to concomitant symptoms.

From Table I it is apparent that lactogenic hormone is of proved value in controlling excessive uterine bleeding. It was equally effective in controlling menorrhagia, whether functional or organic in origin.

Of the 17 women suffering from functional menorrhagia, i.e., menorrhagia associated with no pathologic manifestations, two failed to respond favorably to the hormone therapy. All the patients in this group gave a history of excessive bleeding for at least one cycle prior to their appearance in the clinic. In fact, a majority of the patients offered the information that the excessive menstrual periods were of long duration and the interval between the menstrual flow was obvious only by its brevity. Uterine biopsies taken in this group of patients on the first day of menses exhibited predominately an estrogenic or cystic glandular hyperplastic endometrium, although several cases were observed where menorrhagia was associated with a secretory endometrium. Daily injections of 100 I.U. of prolactin were administered during the period of uterine bleeding. The clinical success of this mode of therapy was indicated by the cessation of bleeding that occurred in all but two of the 17 patients treated. The severity of bleeding in subsequent cycles depended upon the regimen that was employed. In those cases where prolactin was injected on the first day of subsequent menses and continued for 2 to 3 days, bleeding was well controlled. Of those patients

who did not receive further treatment after one successful therapeutic course with prolactin, five had normal cycles and two reverted to their original condition of excessive and prolonged uterine bleeding.

Menorrhagia associated with fibromyoma of the uterus responded very satisfactorily to prolactin therapy. These patients were more resistant to treatment than those with functional menorrhagia and required daily doses of 100 to 200 I.U. of prolactin for a period of 4 to 8 days, whereas patients with functional menorrhagia required only 100 I.U. per day for 3 to 6 days. All the patients in this group had been suffering with menorrhagia for at least three months and one third of these patients bled almost continually. The clinical results with prolactin were pronounced, although not as favorable as in the patients with functional menorrhagia. Three patients failed to respond satisfactorily to prolactin therapy. As has been mentioned before, prolactin was not administered to these patients for the purpose of causing a regression of the uterine fibromyomas, but was employed so that the patient might be placed in proper physical condition to withstand the necessary surgery. This procedure was resorted to since clinically, many of these patients exhibited a severe secondary anemia as a result of their bouts of excessive uterine bleeding. In no instance in cases of fibromyomas of the uterus does the use of prolactin imply a substitute for surgery.

Menorrhagia noted in the presence of cystic follicles in the ovaries likewise required persistent prolactin therapy to control the excessive uterine bleeding. The presence of cystic ovaries was determined by palpation and then confirmed by laparotomy, or was ascertained by surgery alone. In those cases in which prolactin was effective, it was necessary to use daily doses of 100 to 200 I.U. of prolactin for periods of 5 to 8 days before bleeding could be controlled. Inasmuch as all the patients in this group were subject to pelvic surgery, data on the menstrual periods following therapy is meager. However, it may be said that three patients who had been successfully treated with one or two courses of prolactin had 2 to 4 normal menstrual periods prior to the time of their operations.

Menorrhagia when seen with concomitant chronic pelvic inflammatory disease, was aided by prolactin therapy, although we had our greatest percentage of failures in this group of patients. Two patients did not respond to prolactin, and in three, prolactin induced a diminution of bleeding but not complete arrest. However, of the nine patients that responded to prolactin therapy, all but one resumed normal menstrual periods after two or three courses of treatment. This ability of prolactin to exercise curative effects after cessation of therapy is of importance and implies a degree of permanency in the corrective effect of prolactin upon excessive uterine bleeding in certain selected cases.

Fourteen patients, although complaining of menorrhagia, also experienced severe dysmenorrhea either during the entire menorrhagic period, or on the first few days of the menstrual flow. Of these women, eight obtained relief from their painful menstruation accompanied by cessation of the abnormal bleeding. Three of the six patients not obtaining relief from dysmenorrhea with prolactin, did receive prompt relief from their menorrhagic syndrome.

In the treatment of threatened or habitual abortion, the results observed with prolactin were at times promising and at times disappointing. Six cases in all were treated. All the patients gave a history of previous pregnancies which in four patients were associated with missed or habitual abortion. In three patients, all having previous abortive

interruptions of pregnancy, the results were spectacular. When first seen, these patients had severe abdominal cramps accompanied by profuse uterine bleeding. After daily doses of 400 I.U. of prolactin (200 I.U. administered twice per day) for 3 to 4 consecutive days, abdominal cramps became quiescent and bleeding ceased. One patient with a history of two previous abortions experienced an attack similar to those which had precipitated the other abortions, but this time she received a course of prolactin therapy. All threatening symptoms subsided after this one series of injections, and she delivered a normal infant at term several months later. In the other two cases of threatened abortion that were successfully controlled by prolactin, it was necessary to administer prolactin during 4 to 6 successive attacks of severe abdominal cramps and bleeding. Immediately after an intensive but brief course of prolactin treatment, the muscular contractions subsided and bleeding was suppressed. In these latter two cases, one viable infant was delivered at term to a woman who had not been able to carry her pregnancy to term in three previous instances. Prolactin had been administered to this patient at each one of several seizures of threatened abortion and had adequately controlled her adverse symptoms. The other patient who had responded favorably to prolactin when subjected to threatening seizures finally delivered a viable 7-month fetus following a short period of severe uterine contractions and bleeding. This premature delivery could not be prevented since the patient failed to inform us of her condition early enough so that effective prolactin treatment could be instigated. Prior to this, the patient had had four seizures of cramps and bleeding which had been completely controlled by prolactin. The three cases that did not respond to prolactin therapy aborted during treatment. It is conceivable that in these cases some untoward factor was involved and/or the prolactin injections were started before their maximal influence could take effect and their further action was interrupted by the spontaneous abortion.

Prolactin when administered to normal cyclic women in doses of 300 to 500 I.U. per week for periods of 7 to 10 weeks, did not have any appreciable effect upon the length of the cycle, amount of bleeding or condition of the endometrium. Uterine biopsies taken at various intervals during the period of lactogenic therapy microscopically did not show any deviation from the normal. Two of the women who had been menstruating regularly from a progestational endometrium continued to do so during the administration of the lactogenic hormone. In addition, it might be said that the regularity of these cycles was not disturbed, and there was no evidence of an atrophic endometrium resulting from the continued prolactin medication. The third patient, exhibiting regular cycles, but whose endometrial studies indicated that she was subject to anovulatory cycles, continued to menstruate regularly without alteration of the usual endometrial morphology. In this patient, uterine biopsies, taken prior to treatment with lactogenic hormone on the first day of menses, revealed a proliferative or estrogenic endometrium. This was not altered in subsequent menstrual bleeding during which repeated injections of prolactin had been administered over a period of seven weeks. In addition to these data, observations made in the group of menorrhagic patients also indicated that prolactin exerted little if any effect upon the morphology of the endometrium. Uterine biopsies taken from many of the menorrhagic patients before commencement of prolactin therapy showed predominately an estrogenic, or proliferative type of endometrium. The prolactin therapy which

successfully controlled the excessive uterine bleeding did not bring about any change in the morphologic appearance of the menstrual endometrium, regardless of its histologic make-up before treatment.

Discussion

The control of uterine bleeding by lactogenic hormone raises the question of its possible mode of action. Evidence from animal experiments of earlier investigators and also endometrial studies in the human have indicated that prolactin might conceivably have an antigonadal action. This has been demonstrated by the action of prolactin in decreasing gonadal size in fowls[8] and suppressing estrous cycles in rats.[9-12] In the human, endometrial studies[13-15] have shown that only a relatively small number of women ovulate during the period of lactation. In addition, those women not ovulating, while exhibiting a proliferative endometrium, show one of an early differentiating type, or one associated with low ovarian activity.

In contradistinction to the supposed ovarian negating action of prolactin, recent experimental evidence has shown that the suppressing effect of prolactin upon the estrous cycle of the rat may be ascribed, not to the inhibitory effect of prolactin upon the ovary, but actually to its ability to prolong and maintain the function of the corpus luteum. Administration of lactogenic preparations to adult female rats results in cessation of estrous cycles with the persistence of one crop of active corpora lutea.[10] Evans, et al.,[16] showed that the corpora lutea persisting during lactogenic administration are physiologically active and will induce deciduomata formation in hypophysectomized adult rats. It remained for Astwood[17] to postulate and demonstrate the presence of a third gonadotropic hormone, luteotrophin, which regulates the activity and maintains the function of formed corpora lutea. Since purified lactogenic preparations are capable of maintaining active corpora lutea in the rat, the lactogenic hormone has become allied with the luteotrophic hormone of Astwood.

In considering which one of these properties, ovarian negating or luteotrophic action attributed to prolactin, is the modus operandi in controlling uterine bleeding, it is difficult to reconcile our results with the ovarian negating action of prolactin. In our study of women with normal cycles and those suffering with menorrhagia, massive doses of prolactin did not in any way alter the cyclic manifestations, or cause retrogressive changes to take place in the endometrium. There was no evidence of gonadal inhibition as determined by repeated examinations of the uterine scrapings and operative specimens of the ovaries. On the other hand, it is conceivable that the lactogenic preparations are effective in controlling abnormal uterine bleeding through their luteotrophic properties. It is possible that the administration of these pituitary extracts enhances the production of the corpus luteum hormone or hormones, and provide thereby a proper hormonal balance for the

control of menorrhagia. This seems to be the most logical explanation of the satisfactory results in which not only menorrhagia was controlled, but threatened abortion was held in abeyance.

Summary

1. Menorrhagia, either functional or organic in nature, was favorably influenced by administration of lactogenic preparations extracted from the pituitary gland. Menorrhagia associated with uterine fibromyomas, cystic ovaries, or chronic pelvic inflammatory disease was suppressed in the majority of patients by administration of prolactin. Those patients, however, in the latter two categories were more resistant to therapy. Normal cyclic bleeding followed cessation of prolactin therapy in many of the patients receiving one or more courses of treatment. This permanency or semipermanency in the effect of prolactin afforded a sufficient interval to enable the patient to undergo a more strenuous regime to correct the underlying cause of the excessive uterine bleeding.

2. Some success was obtained in mitigating dysmenorrhea by prolactin therapy when it was associated with excessive uterine bleeding.

3. In addition, the signs and symptoms of threatened abortion were alleviated by administering prolactin to 3 of 6 patients giving a history of previous abortive interruptions of pregnancy.

4. Administration of lactogenic preparations to normal cyclic women did not have an appreciable effect upon the length of cycle, menstrual bleeding or morphologic appearance of the endometrium.

5. It is suggested that the effectiveness of lactogenic hormone in controlling uterine bleeding is probably linked with its luteotrophic properties.

6. In view of the innocuous effect of prolactin upon the normal menstrual cycle and corrective action in metropathic menorrhagia, we find its use is warranted in the control of excessive uterine bleeding.

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CESAREAN SECTION UNDER CONTINUOUS CAUDAL ANALGESIA

A Supplementary Report

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IN A preliminary report[1] the use of continuous caudal analgesia in 50 cases of cesarean section was reviewed. We have added 62 cesarean sections to our series and herewith present a report of our observations of the total of 112 cases. Seventy-three of the patients were operated upon at the Philadelphia Lying-in Hospital, 7 at the Jefferson Medical College Hospital, and 6 at the Philadelphia General Hospital. An additional 22 cases were managed by Dr. Edwards and Dr. Hingson at the Marine Hospital, Staten Island, and 4 cases are from Dr. John C. Hirst's service at the Preston Retreat, Philadelphia.

TABLE I. INDICATIONS FOR OPERATION

Disproportion, twin pregnancy, toxemia	1
Disproportion, pre-eclamptic toxemia	1
Disproportion, previous section	11
Disproportion, pulmonary tuberculosis	1
Disproportion (cephalopelvic)	62
Diabetes	2
Eclampsia	1
Pre-eclampsia	5
Multiple uterine fibroids	4
Previous hysterotomy	2
Rheumatic heart disease	3
Heart disease	8
Previous difficult delivery	3
Uterine inertia	1
Epilepsy	2
Severe contractile burn scar of perineum	1
Advanced pulmonary tuberculosis	3
Premature separation of placenta	1

The usual indications for cesarean section are listed in this table. We had only one opportunity to give continuous caudal analgesia when cesarean section was performed because of premature separation of the placenta, and the result was entirely satisfactory. We were particularly impressed with the prompt contraction of the uterus following removal of the child and the partially separated placenta. It has been our experience that good uterine tone does not exist when cesarean section for premature separation is performed under general anesthesia.

The following contraindications to the use of continuous caudal analgesia in cesarean section are essentially the same as in vaginal delivery:

1. Gross deformities of the spine, particularly of the sacrum (occur less than once in 200 cases).

2. Tumors of the spinal canal, including pilonidal cysts.

3. Local infections around the sacral hiatus.

4. History of sensitivity to one of the cocaine derivatives or their substitutes.

5. Profound anemia, unless supplemented with transfusion and oxygen inhalation.

6. Placenta previa. We have consistently hesitated to use this technique in placenta previa because of possible hemorrhage associated with relaxation of the cervix. It should never be used if the patient is in labor, but we believe it would not be contraindicated if the patient is not in labor and the cervix is fairly thick. We have not had the opportunity of using it in such a case.

7. Hysterical patients, or those physically unsuited. Patients with vasomotor instability or of low mentality, because of a fear of being conscious during the operation, are poor subjects and do not cooperate well.

8. Extremely obese persons in whom the sacral hiatus cannot be palpated.

9. A low lying dura is an absolute contraindication. If the needle should enter the dura and spinal fluid is aspirated, the method should be discontinued as this would result in a total spinal anesthesia.

10. Patients who have a glandular imbalance. In our series both of the patients who had a severe drop in blood pressure showed signs of glandular disturbance.

Preoperative Preparation of the Patient

We believe preoperative preparation is particularly important when a patient is to remain conscious during a surgical procedure. Several points must be considered.

1. Mental reassurance is necessary. Because of the wide publicity given to this new method, facts are often distorted, and as a result some patients fear "a spinal." A careful explanation of the method and procedure before operation usually allays any fear and in every instance postoperatively the patient is enthusiastic about the results. The husband should be informed that at least a half hour must elapse before the operation can be started so that he will not expect her to return to her bed in the usual short period of time. Many patients who had a previous cesarean section under gas-ether anesthesia remarked how much smoother their convalescence was following continuous caudal analgesia.

2. The patient is given 1½ grains (0.1 Gm.) of a barbiturate the previous night and again one hour before operation. This brings her to the operating room in a quiet and cooperative mood for the administration of the drug.

3. Adequate fluid intake preceding operation is important. All cesarean section cases should have blood typing and cross-matching done previously and it is advisable to have plasma available.

4. Soapsuds enema and catheterization with an indwelling catheter is an important part of preoperative preparation.

5. Absolute quite must be maintained in the operating room and the patient should be reassured by the anesthetist throughout the procedure.

Technique

The following is the technique of administering continuous caudal in cesarean section, which varies somewhat from that followed in vaginal delivery.

1. One and five-tenths per cent metycaine in isotonic solution of sodium chloride or isotonic solution of three chlorides (Ringer's solution) is prepared.

2. The continuous caudal needle is inserted and the apparatus adjusted as for obstetric analgesia.

3. An initial test dose of 8 c.c. is administered with careful check by aspiration to ascertain whether or not the needle is within the subarachnoid space or a blood vessel. In this injection of 8 c.c. we are now adding 50 mg. of ephedrine hydrochloride, except where a hypertension is present, to preclude any drop in blood pressure. The hydrochloride solution is miscible with the Ringer's solution, whereas the sulfate is not as readily absorbed and is more likely to give side reactions.

4. A supplementary dose of 40 to 60 c.c., depending on the size of the patient, is administered. The patient is then placed on her back in a 5° Trendelenburg position and the level of analgesia is tested in twenty minutes.

5. If the level of analgesia has not risen above the umbilicus on both sides, a third dose of 20 to 40 c.c., according to the need of the patient, is administered.

6. When the level of analgesia on both sides is complete to the height of the eighth dorsal segment, the operation may be started. This level is usually attained about thirty minutes after the first injection. In debilitated patients, seriously ill with tuberculosis or heart disease, the procedure should be instituted forty-five minutes to one hour before operation and the level of analgesia developed more slowly.

7. In cesarean section patients we have been giving oxygen routinely for approximately ten minutes prior to delivery of the child. This has been found especially valuable in cases of threatened abruptio placentae, toxemia, and cardiac disease. We have observed that if the blood pressure drops and there is any deviation from normal in the fetal heart sounds, they will return to normal within one or two minutes following elevation of the patient's legs, the giving of a supplemental dose of ephedrine, and inhalation of oxygen.

The time required before absence of sensibility to pain is attained varies. The operation should never be started before the level of analgesia is correct and the time required for this should not be hastened by unnecessary and repeated injections of metycaine. In our series the minimum time required before starting the operation was ten minutes; the maximum time, one hour and twenty minutes; and the average time, thirty-four minutes.

The patient who required one hour and twenty minutes before the drug had reached the desired level, had been in the hospital eight weeks with severe cardiac disease. At the time of operation she was very orthopneic and could not be placed flat on the operating table nor in the desired 5° Trendelenburg position. Consequently, a much longer than average time elapsed before the analgesia reached the desired level.

Postoperative Care

At the conclusion of the operation the patient is given ¼ grain of morphine sulfate hypodermically. This eases the incisional pain as the analgesic effect subsides.

Recently, we have been allowing the patient a soft or full house diet the same noon or evening of operation. This regime has decreased our postoperative distention to a minimum. Most patients have had no gas pains and their convalescence has been accelerated.

Complications Associated With Continuous Caudal Analgesia in Cesarean Sections

1. Drop in blood pressure. The average drop in systolic pressure was 22 mm. which is less than the 26 mm. previously reported. Two patients had a severe drop in blood pressure which may have been due to sensitivity to the drug unrecognized prior to operation or to a glandular imbalance, of which both patients showed positive signs. We believe the improvement may be attributed to the use of 50 mg. of ephedrine hydrochloride given with the initial injection of 8 c.c. of metycaine. The more recent cases showed less drop in blood pressure, their average being 14 to 16 mm. of mercury. We have found that the fall in blood pressure is in direct proportion to the height of ascent of the nerve block in the peridural space and to the pharmacologic efficiency of the drug. In those instances in which there is a rather sudden drop in systolic pressure, the elevation of the feet and legs to a right-angle position in relation to the trunk, thereby producing an autotransfusion from the greatly dilated venous system of the extremities, will dramatically raise the blood pressure 20 to 40 points within less than three minutes. The legs can then be returned to their usual position slowly. The blood pressure can be maintained by a 5° Trendelenburg position of the patient. However, in refractory cases of hypotension, the use of 25 and 50 mg. (⅜ and ¾ gr.) of ephedrine hydrochloride intravenously will raise and maintain the blood pressure at a safe level. This initial fall in blood pressure is the most serious complication associated with the technique. It should be diligently watched for, since it occurs in about 25 per cent of cases from 12 to 30 minutes after the initial injection. The majority of these blood pressure drops have occurred just as the patient was being turned from the lateral Sims' position to her back. None of our cases showed any postoperative blood pressure abnormality.

A very interesting observation in every instance of cesarean section as well as in vaginal delivery, is the immediate rise in the systolic blood pressure, within seconds following removal of the child from the uterus. This return to the normal preoperative level varies from 10 to 60 mm. of mercury and may be attributed to the decrease in the vascular bed with the closure of the arteriovenous vessels of the uterus.

2. We have used the malleable needle in all cases but two. In the two cases the ureteral catheter technique was followed. We have had no instance of needle breakage. As the malleable needle becomes more disfigured and bent during cesarean section than during the usual vaginal delivery, it was never used more than once or twice for this procedure and was then discarded.

3. Morbidity. There were three cases who had a febrile postoperative course. One morbidity was due to a mild endometritis following a ten-hour labor with ruptured membranes before operation. The other 2 cases had postoperative pyelitis which cleared up after routine treatment was instituted.

4. Bladder dysfunction. In no instance was catheterization necessary beyond what is usually required following cesarean section. There was no post-partum bladder paralysis.

5. Infection at the site of the needle insertion or in the peridural space was not present in our series. After the initial dosage of 8 c.c. of metycaine the skin area about the needle is covered with a 5 per cent sulfathiazole or merthiolate ointment before the patient is turned on her back. We believe this technique minimizes the hazard of infection entering the site where the needle punctures the skin.

6. Blood loss. The average estimated blood loss in all of our cases was 100 c.c. This was a definite decrease over cesarean sections previously performed under general anesthesia. An ergot and posterior pituitary preparation is employed intramuscularly following extraction of the child.

7. Other complications, such as headache, backache, or nausea and vomiting, were minimal. Vomiting occurred in 10 per cent of the patients during the administration of the drug. Whether this was due to anxiety or to the action of the drug on the maternal organism is not known. Several headaches occurred in patients in whom the solution was injected rapidly, in an attempt to gain a higher level of analgesia. However, they were all transient in duration and soon disappeared.

There were no maternal deaths in our series. One fetal death occurred which we do not believe can be attributed to the analgesic agent. This baby was delivered of a seriously toxic mother at 5½ months' gestation and succumbed within eight hours after birth.

Comment

In 108 cases, perfect analgesia was obtained. Three failures were attributed to inability to insert the needle, and 1 was due to malformation of the sacrum.

TABLE II. TYPES OF OPERATION

Low classical and sterilization	21
Low classical	54
Low segment operation	27
Low classical, myomectomy	3
Low classical, salpingectomy	1
Waters modification of Latsko	6

The type of operation depended upon the individual patient and whether she was in labor or whether an elective section was to be performed. The operating time varied from fifteen to seventy-five minutes, with the average length of time thirty-eight minutes. The safety of continuing repeated injections as long as required, thus obviating the necessity to hasten the operation, is the outstanding feature of this method of analgesia.

Metycaine was used in all of the cases. The minimum amount necessary was 25 c.c., the maximum 370 c.c., with an average of 76 c.c.

We feel that this is one of the best methods that we have tried and is perfectly safe when administered by a trained person in a well-equipped maternity department. Our decision is influenced by the improved convalescence of the mother with absence of postoperative discomfort, the immediate cry of the baby at birth, and the fact that no baby in our series required resuscitation.

As we have continued our study, we have become more impressed with the following features of this method: First, the drop in blood pressure has been materially reduced by the use of ephedrine hydrochloride in the initial dose of metycaine; second, the injection of the drug should be slow, and ample time given to allow perfect analgesia before the operation is started; third, the level of analgesia is maintained easily regardless of the length of operation; fourth, the use of this method is especially advantageous in cardiac cases, toxemias, and respiratory infections; and fifth, the families of the patients are enthusiastic and appreciative of the rapid and smooth convalescence of mother and baby.

Summary

Cesarean section under continuous caudal analgesia was performed in 112 cases with perfect results in 108. There were 4 failures attributed to inability to introduce the analgesic agent into the sacral canal.

There were no maternal deaths, and no serious postoperative complications. There were 3 cases of morbidity, but these are not attributed to the use of the analgesia.

One baby death occurred in a 5½ months' gestation and the other 111 babies were discharged from the hospital in good condition.

Due to an improvement in technique, the blood pressure drop in our recent cases was less than previously reported.

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ACUTE PELVIC THROMBOPHLEBITIS TREATED WITH CONTINUOUS CAUDAL ANESTHESIA

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THE literature during the past year has been replete with reports of continuous caudal anesthesia in obstetrics, but there has been very little written on this procedure as a form of therapy in other conditions.

During the past six months at Providence Hospital, we have used this method in ten cases of acute pelvic thrombophlebitis, with very good results.

While we realize that this is a small series of cases, the results obtained warrant its further investigation by other observers.

The technique and contraindications are essentially the same as in obstetrics.

Following are two fairly typical case reports:

CASE 1.—Mrs. M. B., a 24-year-old primipara, had vaginal bleeding three weeks before her expected date of confinement and was delivered by classical cesarean section for ablatio placentae. Postoperatively, a lobar pneumonia developed which responded to sulfonamide therapy. She had a wound infection which was still draining when we first saw her, six weeks post partum. At this time, there was an acute pelvic thrombophlebitis of three days' duration. The whole left leg was swollen, blanched and extremely painful. Her temperarute was 102° F., and the pain was unrelieved by ¼ gr. doses of morphine.

That evening a caudal anesthetic was started and continued for four hours. Following this the pain was permanently relieved, the extremity became warm, and the swelling began to subside.

The next day her temperature was 99.2° F., and there was slight ankle edema.

She left the hospital 48 hours following the caudal treatment, symptomatically cured.

CASE 2.—Mrs. H. J. S., developed an acute pelvic thrombophlebitis of the left leg three weeks postoperatively following a supravaginal hysterectomy.

She was readmitted to the hospital and a caudal anesthetic administered.

For 24 hours she had complete relief of pain, but the elevated temperature and swelling persisted.

Forty-eight hours after the original caudal injection, another was given, following which her symptoms and temperature completely subsided.

This was the only case in this series in which a second treatment was necessary.

We would first like to describe what we mean by acute pelvic thrombophlebitis. This is that type of intravenous clotting which is associated with inflammation of the vein wall (thrombophlebitis) and we will also only consider the most common clinical form, thrombophlebitis of the femoro-iliac vein, which gives us the typical picture of phlegmasia alba dolens. No attempt will be made to discuss the other types of intravenous thrombosis, which are equally important, such as partial or complete venous occlusion by an intravenous clot, unassociated with any inflammation of the vein wall (phlebothrombosis), or of thrombophlebitis of a superficial vein or of suppurative thrombophlebitis, all of which we believe require surgical treatment (ligation).

There is little difficulty in recognizing phlegmasia alba dolens; the patient is quite ill, has fever, a marked amount of pain in the affected limb and the extremity is swollen and white. Ordinarily, with elevation of the affected limb, rest and external heat, we would expect persistence of fever for several weeks and of edema for several months, with a long period of partial disability. However, with the use of sympathetic block by caudal anesthesia we have definitely reduced the time element in the alleviation of these symptoms to a matter of days.

A concept of the underlying etiological factors and pathology involved will give a better understanding of the rationale of this form of nerve block as a method of treatment for this condition. We will discuss the causes of phlegmasia alba dolens first in general, and then specifically.

In general, this is the most common form of thrombophlebitis because there is greater circulatory retardation in the lower extremities postoperatively or post partum, compared with the upper extremities. These patients will lie quietly in bed, seldom moving their lower extremities. Also Fowler's position causes circulatory retardation in the veins of the lower extremities, which is made worse by flexing the knees. Another factor in the movement of blood in the venous system is the negative pressure in the thorax. Postoperatively deep breathing is limited by the patient because it is painful, resulting in a decrease in the intrathoracic negative pressure and so favoring circulatory stasis. Increased abdominal tension also causes circulatory stasis in the lower extremities by direct pressure, due to too tight bandaging, or to gas or fluid within the intestine associated with ileus. The clot occurs more often in the left lower extremity than the right because the left common iliac vein is smaller than the right, it joins the inferior vena cava at a more acute angle than does the right, and it is crossed over by the iliac artery.

Specifically there are certain factors which predispose to the formation of a clot, the first is an inflamed vein wall and the next most important factor is tissue injury due to operative or accidental trauma, or by invasion of inflammation, or malignant disease. The toxic substances absorbed from this damaged tissue decreases the albumin content and increases the globulin content of the blood so that their ratio is dis-

turbed. This results in changes in the electrical charges of the formed blood, so that instead of normally repelling each other they become attracted to one another and so form a center for clot development. This explains why the platelets and erythrocytes and leucocytes show an increased agglutination tendency.

Pathology of Thrombophlebitis

It has been generally accepted that the edema in thrombophlebitis is due to increased venous pressure, produced by the blocking of the large vein draining the extremity by the clot. This is not true, because these patients can be relieved of their edema often within a week, long before the clot has disappeared. An understanding of the true pathology underlying "milk leg" will show how logical the use of sympathetic block is in these cases.

In thrombophlebitis there is set up in the thrombophlebitic segment impulses which are carried over the sympathetic nervous system producing spasm of the arterioles and venules. Normally, there is an interchange of intravascular and perivascular fluids. Fluid leaves the vascular tree at the arteriole extremity of the capillary because of filtration pressure. Fluid returns to the vascular system through the lymphatics and by absorption into the blood stream at the venule end of the capillary—this fluid exchange is normally in balance. However, when we have a spasm of the arteriole, the blood flow through the capillary is diminished and a relative anoxia occurs, this anoxia increases the permeability of the capillary endothelium and there is an abnormal exudation of fluid from the vascular system into the perivascular spaces. Once the fluid gets out, it has difficulty in getting back because the pump responsible for the movement of lymph, namely arteriolar pulsation, is no longer present so that fluid getting into the lymphatic system is not transported back to the blood vascular system. Also the increased pressure on the venule end of the capillary tends to prevent the normal absorption of fluid from this site.

Therefore, if we can prevent or break the vasoconstrictor impulses passing to the arterioles and venules from the sympathetic ganglion, the blood supply to the capillaries is re-established. The anoxia of the capillary wall is relieved by the return of normal oxygen tension and the previously increased permeability of the capillary is prevented. The excessive exudation of fluid outside the capillary is stopped. Also the arteriolar pulsation which is responsible for the movement of lymph is re-established so that the fluid can be removed from the extremity. By relieving the spasm on the venule, absorption of the perivascular fluid into the capillary is favored and this is the reason why patients with thrombophlebitis, in whom the thrombus is still present, have relief of their edema following lumbar sympathetic block. The clot has been firmly attached to the vein wall by the inflammatory process and there

is no danger of it breaking loose. With the return of the normal blood supply and vascular balance, the inflammation in the affected vein quickly subsides and the patient is clinically well.

Treatment of Phlegmasia Alba Dolens

Preventive or prophylactic treatment is of first importance. Patients should have their heart conditions corrected as well as possible before delivery or operation, since it is well known that the incidence of thrombosis is much higher in these cases if uncorrected, probably due to circulatory retardation. Correction of varicosities by either compression bandages, or by ligation and injection before delivery or operation is indicated. Foci of infection, obesity, blood dyscrasias (anemic and polycythemic patients have increased clotting tendencies) should all be treated beforehand. During the delivery or operation, we should try to be as atraumatic as possible, since it is the damaged tissue which releases the toxic substances which cause increased clotting tendency.

During the puerperium and postoperatively, normal water balance should be maintained. We should avoid postures favoring circulatory stasis of the lower extremities such as Fowler's position, especially when combined with flexion on the thighs on the trunk, and the knee on the thigh. The patient should actively contract the muscles of the lower extremities by forcefully flexing the feet against a resistance and the legs should be flexed repeatedly. We should also encourage respiratory stimulation by having the patient take ten to fifteen deep breaths every hour, thus the negative pressure in the thorax is increased and this favors the return flow of blood to the heart. Increased abdominal tension should be prevented by avoiding tight compression bandages on the abdomen and by preventing ileus. There is a great tendency after operation for the nurse to apply adhesive as snug as possible to the surgically relaxed abdomen. Ileus can be avoided by observing the period of functional inactivity of the bowel postoperatively, by restriction of what is taken by mouth during this period, the use of prostigmine and rectal tube, or, if necessary, the Wangensteen suction apparatus. Anticoagulants are of value but are not without danger, and should be used prophylactically only in patients with a history of previous intravenous thrombosis.

Thrombophlebitis of the femoro-iliac veins when it does occur either because the prophylactic measures were not used or in spite of them, can be best treated conservatively by caudal blocking of the sympathetics and early mobilization of the extremity. As soon as the swelling and fever have subsided, usually in a few days' time, they are allowed out of bed. They are instructed to wear compression bandages afterwards for a few weeks until the vascular balance is completely reestablished.

Conclusions

We feel that by using the caudal method there are several advantages over the regional sympathetic block of the first, second, third, and fourth lumbar sympathetic ganglia.

Regional injection requires four punctures, caudal but one. We believe that the continuous bathing of the sympathetic chain for several hours is preferable to the one-injection technique necessitated by the regional block method.

In caudal nerve block we can tell when the needle is correctly placed by the classical signs, i.e., sciatic pain, progressive regional anesthesia, sphincter relaxation and finally by vasodilatation of the extremities. The same cannot be said of sympathetic nerve block because one cannot be sure if all the ganglia have been correctly injected.

In acute thrombophlebitis, we give 30 c.c. (low caudal) every hour until four doses have been given. With this intermittent method of injection, if there is any tendency for the vasoconstriction to re-establish itself after the effect of the drug wears off, we can immediately release the impulse by the next injection. Following the last injection, the needle is removed.

Finally, we feel that this is another form of therapy to be used in the treatment of acute pelvic thrombophlebitis and that it offers certain advantages over regional sympathetic block.

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VAGINAL ANTISEPSIS

A Comparative Study of Bimerphen Solution* in 910 Consecutive Deliveries

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THE purpose of the present study is to compare Bimerphen solution with other antiseptics which have been used for vaginal instillation prior to delivery.

There has been a great deal of controversy regarding the value and rationale of using predelivery antiseptic vaginal instillations, but the results from many studies[1-6] definitely establish the value of this procedure. Morbidity and mortality figures released from several centers prior to the use of vaginal instillation indicate that a figure between 15 and 20 per cent morbidity is to be expected. Following the adoption of this procedure, the figures show a marked reduction in morbidity and mortality.

During the third trimester of pregnancy, there is an increase in vaginal secretions which is accepted as a normal physiologic reaction. These secretions are usually alkaline in character and in most instances show a pH well above 6.0. At this pH or above, abnormal bacterial inhabitants and pathogenic organisms (aerobic and anaerobic) are provided with an environment conducive to their growth and propagation, thus presenting a potential source, at least, of post-partum infection.

Despite the arguments presented against the use of vaginal instillations,[1] the statistics from various clinics indicate that the procedure is of value, regardless of the antiseptic used.

In 1926, Schwarz and Brown[2] initiated the routine use of mercurochrome, iodine and glycerin, and in 1930, 1 per cent neutral acriflavine in glycerin. Morbidity figures were reduced by one-half.

Brown[3] in 1940, reported 13 deaths in 9,529 deliveries prior to vaginal antisepsis, but after the advent of vaginal instillations, no deaths due to sepsis occurred in 12, 913 deliveries.

Mayes[1] reports that at the Brooklyn Methodist Hospital where the mercurochrome technique had been in use for five years, no deaths occurred from sepsis in 5,648 deliveries and the morbidity figure for the period was 2.3 per cent.

Tritsch[4] in a comparative study using amphyl and 4 per cent aqueous mercurochrome reported equal efficiency in both preparations. The incidence of infection in spontaneous deliveries was 5.4 per cent and

*Bimerphen solution, supplied by the Medical Research Division, Sharp & Dohme, Glenolden, Pennsylvania, is a solution of hexyl m-cresol 1:1,000 and phenyl mercuric acetate 1:1,000 in an aqueous propylene glycol base.

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in operative deliveries 7.4 per cent; the incidence of infection in primiparas was 9.2 per cent (due to greater operative procedures) and 4.6 per cent in multiparas.

Ziegler and Austin[5] reported a total of 5,140 deliveries and were able to show a decrease in morbidity figures after the use of tincture of merthiolate 1:2,500 solution as vaginal instillation. In 1932, prior to the use of the solution, the morbidity was 15.21 per cent, while in 1937, following the adoption of the procedure, the figure was 9.16 per cent (including 287 cases not receiving the instillations).

Mayes,[6] reporting the use of 4 per cent aqueous mercurochrome solution in 13,763 deliveries at the Methodist Hospital, Brooklyn, shows a reduction of morbidity from 14.8 per cent to 5.3 per cent. Two deaths from sepsis occurred in 25,347 vaginal deliveries while none have occurred in the last 11,000 deliveries. They have also used 1:1,000 solution of zephiran on 837 cases with a morbidity rate of 8.7 per cent.

Here at Hahnemann Hospital a previous series of 1,000 patients was studied in which 'S. T. 37' hexylresorcinol solution was used. A morbidity figure of 7.0 per cent was obtained. Four per cent mercurochrome was also tried on 326 cases showing a morbidity figure of 6.94 per cent. Ten per cent mercurochrome, used as an external spray to the genitalia only, produced morbidity figures of 10.28 per cent in 523 patients. Our experience with the use of amphyl, with one routine vaginal examination allowed for each patient, showed morbidity figures of 12.02 per cent in 707 patients. No vaginal examinations were permitted when the other antiseptics were used.

Assuming that vaginal antisepsis is rational and a definite aid in the reduction of morbidity, we feel that the requirements for a suitable agent should meet the following:

1. Safety to mother and child.
2. Germicidal and bacteriostatic.
3. Rapid in action.
4. Easy to apply.
5. Does not stain linens, etc.
6. Readily available.
7. Economical.

Bimerphen solution is a combination of hexyl m-cresol 1:1,000 and phenyl mercuric acetate 1:1,000 in 75 per cent propylene glycol. The combination of the two compounds supplies marked bactericidal as well as great bacteriostatic activity. The solution is effective in the presence of serum or other body fluids. The pH of the solution is 3.6 which provides additional unfavorable environment for the growth of pathogenic bacteria. The germicidal activity of propylene glycol is well recognized. Bimerphen solution does not stain tissues or bed linens.

The technique of administration was as follows: one-half ounce Bimerphen solution was instilled into the vagina with a sterile Asepto

syringe. The original instillation was given on admission to the floor and repeated in four hours if the patient was undelivered, and repeated again in four hours if the patient was still undelivered.

These 910 consecutive cases were divided on the basis of number of doses of bimerphen received prior to delivery. Morbidity figures are based on two or more temperatures of 100.4 or more, occurring at any time in the puerperium excluding the first twenty-four hours after delivery.

Table I, a summary of pertinent data, reveals some rather interesting information. Although we were somewhat handicapped in carrying out this study due to the lack of help, rapid turnover in personnel, and loss of our obstetric resident for a period of time, we were gratified at the results obtained.

TABLE I. SUMMARY OF DATA COLLECTED ON PATIENTS TO WHOM 1-2-3 DOSES OF BIMERPHEN SOLUTION WERE ADMINISTERED

NO. AND PERCENTAGE OF PATIENTS IN EACH GROUP	3 DOSES		2 DOSES		1 DOSE		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%
	297	32.6	215	23.6	398	43.7	910	100.0
At term	279	94.0	197	91.6	370	93.0	846	92.9
Premature	18	6.0	18	8.4	28	7.0	64	7.1
Primiparas	167	56.2	84	39.1	78	19.6	329	36.15
Multiparas	130	43.8	131	60.9	320	80.4	581	63.85
Operative incidence	16	5.3	2	0.9	2	0.5	20	2.19
Perineal injuries (including episiotomy)	178	59.9	113	52.5	149	37.4	440	48.3
Morbidity (total)	20	6.7	16	7.44	25	6.28	61	6.70
Morbidity (pelvic)	16	5.38	14	6.51	22	5.53	52	5.71
CAUSES OF MORBIDITY								
A. Endometritis	12	60.0	8	50.0	16	64.0	36	59.0
B. Parametritis	1	5.0	2	12.5	3	12.0	6	9.8
C. Infected perineum	3	15.0	3	18.75	2	8.0	8	13.1
D. Medical, etc.	4	20.0	3*	18.75	4*	16.0	11	18.0

*Includes exacerbation of gonorrheal salpingitis—1 case.

The majority of the group receiving three instillations were primiparas (56.2 per cent). This fact was due to the longer labor usually making them available for three doses. Those receiving but one dose were delivered within the first four hours after admission; this group shows a heavy percentage (80.4 per cent) of multiparas.

The perineal injury group, which includes episiotomies, first, second, and third degree lacerations, revealed an interesting finding. The group receiving three doses of Bimerphen solution (32.6 per cent) showed a morbidity of 5.38 per cent while the group receiving but one dose (43.7 per cent) had a morbidity of 5.53 per cent. The operative incidence of the first group was 5.3 per cent while in group three, it was 0.5 per cent. These figures would seem to point to the effectiveness of Bimerphen when administered in at least three doses. In spite of the fact that the operative incidence was some ten times greater in the first group and the percentage of perineal injuries was significantly greater, the morbidity figures closely approximate each other—5.53

and 5.38 per cent. It is well established that the greater the operative incidence and perineal injuries, the higher the morbidity figures.

There were 440 cases of perineal injuries with a morbidity figure of 6.8 per cent. The group without perineal injury (470) showed a morbidity figure of 4.68 per cent. This comparison bears out our previous statement.

Morbidity causes included endometritis, parametritis and infected perineum. No significant difference in figures was evident in the three groups. Medical, breast, and renal causes were excluded in compiling these figures.

TABLE II. COMPARISON OF RESULTS WITH USE OF VARIOUS ANTISEPTICS

	AMPHYL	10% MERCURO-CHROME EXT. SPRAY	4% MERCURO-CHROME	S. T. 37 SOLUTION	BIMERPHEN SOLUTION
Number of cases	707	523	326	1000	910
At term	684	500	303	917	846
Premature	23	23	23	83	64
Primiparas	264	187	134	389	329
Multiparas	443	336	192	611	581
Forceps	14	8	11	30	17
Versions	4	2	1	2	3
Perineal injuries (including episiotomy)	256	198	144	499	440
Morbidity (total percentage)	20.50	22.30	13.50	12.0	6.70
Morbidity (pelvic percentage)	**12.02**	**10.28**	**6.94**	**7.0**	**5.71**

Table II is a summary of our findings on the use of the various antiseptic solutions over a period of years. Amphyl (morbidity 12.02 per cent) was administered in 707 cases; however, one vaginal examination was allowed in each case. The 10 per cent mercurochrome series (523 cases) showed a morbidity of 10.28 per cent, but the solution was used as an external spray only. In a study of 326 cases, 4 per cent aqueous mercurochrome was instilled, providing a decreased morbidity figure of 6.94 per cent. In the series previous to the present one, we studied 1,000 consecutive cases using "S. T. 37" hexylresorcinol solution with a morbidity figure of 7.0 per cent. The present study with the use of Bimerphen solution in 910 consecutive cases has, under present day difficulties, produced the excellent morbidity figure of 5.71 per cent.

Discussion

The figure of 5.71 per cent morbidity with the use of Bimerphen solution compares favorably with results obtained from other studies. It would appear from our data that three instillations of the solution prove most effective, but even when only one instillation was administered, the morbidity figures are significantly lower than when no antiseptic was used. Mayes,[7] in a survey of 848 diplomates of the American Board of Obstetrics and Gynecology and a study of 236,295

hospital deliveries following the use of vaginal instillations, reports that 60.9 per cent of these individuals used some type of vaginal antiseptic prior to and during labor. From the survey, it was determined that 24 different antiseptic solutions were utilized in a total of 224,575 deliveries. It would appear that the choice of antiseptic is not so important as the fact that the procedure of vaginal instillations should be instituted. Morbidity figures from the many studies indicate a definite reduction following the use of antiseptic vaginal instillations.

One of the most practical features of Bimerphen solution, at the present time especially, is the nonstaining qualities of the material. We feel that this solution meets the requirements set up for an adequate vaginal antiseptic.

Conclusions

1. The routine use of vaginal instillations prior to delivery is a valuable procedure.

2. Bimerphen solution has been found to be at least as effective as other antiseptic solutions.

3. Bimerphen solution is safe for mother and child, is rapid in action, easy to apply, and is nonstaining.

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VITAMIN AND ENDOCRINE THERAPY IN NAUSEA AND VOMITING OF PREGNANCY

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THIS study is based on 100 cases of nausea in early pregnancy. All vomited one or more times each day.

Forty-three received pyridoxine hydrochloride (B_6) alone. The first patients treated received 50 mg. intravenously at a dose which was given as often as the nausea recurred. In some of them 50 mg., gave partial or no relief. They were given 100 mg., with better results. The results with the use of B_6 alone were:

	Completely Relieved	Partially Relieved	Failure
Primigravidas	17	6	2
Multigravidas	6	7	5
Total	23	13	7

A very interesting feature was the disparity in results between the primigravidas and multigravidas.

The patient was counted completely relieved only if no nausea remained. If she experienced some relief but had residual nausea; the result was counted as partial. If the patient felt that she was not benefited or was undecided, the result was counted a failure. If relieved from the nausea but it later recurred between injections, this was counted successfully treated.

Sixty-six patients received B_1 and B_6 in combined doses. The initial doses were 50 mg. of each, but this was increased to 100 mg. of each, after the smaller dose had given indifferent results in some cases.

	Complete Relief	Partial Relief	Failure
Primigravidas	31	6	2
Multigravidas	15	5	7
Total	46	11	9

Of the patients who received B_1 and B_6 in combination, nine had previously received B_6 alone with little benefit.

In these nine patients, four were relieved by the administration of combined vitamins.

The five who failed to be relieved by combined vitamins were given adrenal cortex extract in daily doses of 2 c.c. subcutaneously. Three of these patients said that they felt decidedly better on this treatment and were able to retain food.

Since we failed in some of our early cases with 50 mg. doses of the vitamins, we adopted the procedure of giving both components in 100 mg. doses to patients who had marked nausea. There was often a lag period of 24 to 48 hours after the injection before the patient received maximum benefit.

To conserve drugs, we gave most patients injections only as dictated by the return of nausea.

Six patients were given B_6 in doses of 25 mg. a day orally for one to two weeks. Only two felt that they were definitely benefited, however, and two patients of this group were not relieved by intravenous administration.

Our results with the combined vitamins were even better comparatively than shown in the statistics because we adopted the practice of giving severe cases the combination without preliminary treatment with B_6. The most spectacular results were in those patients who had been vomiting for some time, and probably had developed a definite thiamin deficiency.

Six of the 100 were classed as having pernicious nausea and vomiting of pregnancy. Three were multigravidas and three were primigravidas. The primigravidas and one of the multigravidas were completely relieved. Two of the multigravidas were not benefited by vitamins.

At present we have no adequate explanation for the difference in the results in multigravidas and primigravidas. As shown experimentally, rats that are deprived of pyridoxine die in fits and dogs develop anemia. Its role in human physiology has not been definitely proved, however, the animal experimentation point to it as linked with fat metabolism.

It has been established that thiamin is necessary in certain phases of carbohydrate metabolism. It is easily exhausted in vomiting. For this reason, the results in those people who have vomited for a considerable period are often dramatic. Its exhaustion also leads to the polyneuritis of pregnancy.

The adrenal extract had the following rationale for its use: (1) It is essential in metabolism of all classes of foods; (2) in the laboratory, it has been shown to increase the activity of thiamin. If the adrenals are not secreting properly, then essential links in the metabolic enzyme chain fail.

The number of patients treated with this preparation was too small to permit conclusions.

Summary

Forty-three patients received pyridoxine hydrochloride (B_6) in doses of 50 to 100 mg. intravenously. Of this group twenty-five were primigravidas and eighteen were multigravidas. Eighteen, or roughly three-fourths of the primigravidas were completely relieved, while only six, or one-third of the multigravidas were relieved. Of the seven complete failures, five were multigravidas.

Thirteen of the group had partial relief of which six were primigravidas and seven were multigravidas.

A total of sixty-six patients received combined doses of thiamin hydrochloride and pyridoxine hydrochloride in doses ranging from 50 mg. to 100 mg. of each. Of this group, nine had previously received pyridoxine alone with partial or no relief at all. In this group there were twenty-seven multigravidas and thirty-nine primigravidas.

Thirty-one of the primigravidas were completely relieved; there were two complete failures, while six others had varying degrees but definite relief.

Fifteen multigravidas were completely relieved and seven were not benefited, while five reported partial relief.

Five patients who were not benefited by vitamins were given adrenal cortex extract. The usual dose was 2 c.c. given subcutaneously at daily intervals. Three felt better and were able to retain food.

Conclusions

Thiamin hydrochloride and pyridoxine hydrochloride combined in doses of 100 mg. each, were superior to pyridoxine alone, or to doses of 50 mg. each of the two combined.

The medication was usually given intravenously. If the patient was not benefited by the first injection further treatment was usually futile.

The results in primigravidas were much better than in multigravidas regardless whether pyridoxine hydrochloride was given alone, or in combination with thiamin hydrochloride, for this we have no adequate explanation at present.

Five patients in whom the vitamin treatment failed were given an average daily dose of 2 c.c. of adrenal cortex extract for a few days. Three were able to maintain food when given this medication.

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FURTHER STUDIES ON INTRAUTERINE SULFANILAMIDE PACKS

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PREVIOUSLY this clinic has reported the first work with intrauterine sulfanilamide packs.[1] The principles of intrauterine tamponade and the literature on the subject were reviewed in that paper. In summary, that report demonstrated the superiority of sulfa gauze over plain and iodoform gauze packing on three counts: reduced uterine bacterial contamination, lower morbidity rates, and improved genital hygiene.

Our studies were continued in order to ascertain the most satisfactory form of intrauterine pack for this purpose and to set up standards for commercial preparation.

Several factors required further consideration: (a) The length and size of the gauze, (b) the concentration of the sulfanilamide; (c) the physical state of the gauze, i.e., dry or moist; and (d) the method of preparation for preservation and dispensing. This report deals with a consideration of these factors.

Size of Gauze.—As would be expected in a study of this sort, the number of cases of atonic uteri available for packing was small. By the use of ether, and delaying the post-partum oxytocic, we were able to simulate this pathologic state. The gauze from which the pack was prepared was 5 yards long and 36 inches wide, folded into a 2½-inch pack and saturated with sulfanilamide. The uterus was packed by the previously described technique. The amount of gauze remaining was measured to determine the amount of packing required. In the 32 uteri packed in this study, the maximum length of the 16-fold 2½-inch gauze was slightly over 4 yards and the average was about 3 yards (Table I). Because these were not truly atonic uteri, it seems desirable to recommend a 5-yard pack to permit a good margin of safety.

The Concentration of Sulfanilamide.—The concentrations of sulfa would seem to be fixed by its solubility; however, by varying the preparation procedure, a supersaturated gauze can be made. A 10 per cent impregnation made available to us, yielded approximately 0.7 Gm. per yard. Thus, if one used only the average 3 yards of packing, the quantity of sulfa in contact with the uterine wall would be small. When the concentration was raised to 20 per cent (1.5 Gm./yd.), the gauze became quite stiff and was somewhat difficult to handle.

The packs were left in the uteri for 24 hours and a blood sample was taken at the time of removal. Bacteriologic studies of the previous report[1] demonstrated the bacteriostatic action of the sulfanilamide; consequently these studies were not repeated. Table I records the blood levels with the different types of gauze studied. The consistently

higher level of blood concentration in the 20 per cent pack is not related to the length of pack used; this indicates the advantage of the higher gauze saturation.

Moist Glycerin Packs.—In order to avoid the stiffness of the 20 per cent dry pack, studies were run with moist packs—using glycerin to retain moisture and increase sulfanilamide saturation. This permitted us to use the 20 per cent pack with 1.5 Gm. sulfa per yard. This preparation was very much easier to handle and greatly facilitated packing the uterine cavity.

As noted in Table I, the 20 per cent moist packs gave a slightly higher average blood level than the dry; we are not sure whether this was due simply to a higher concentration of sulfa, to the suspended state of the sulfa in the glycerin, or whether the greater ease of handling

TABLE I

DRY			MOIST		
CASE NO.	LENGTH OF PACK	BLOOD LEVEL 24 MG. %	CASE NO.	LENGTH OF PACK	BLOOD LEVEL 24 MG. %
		10% SULFA			
4	3¼	0.48	1	3	0.24
5	2	1.92	2	2	1.37
7	4	1.2	3	2	1.14
8	2¾	0.35	6	4	1.06
12	4¼	0.94	9		2.05
15	2	1.44	16	3¼	1.8
			17	2¼	1.4
			23	3	2.06
6 Cases Avg.	3.1	1.1	8 Cases Avg.	2.7	1.4
		20% SULFA			
14	3¼	1.78	10	2	1.25
18	3	1.14	11	3¼	2.87
19	2¼	.95	20	3½	5.04
24	2	0.57	21	2¼	4.2
25	4	2.84	22	4	2.78
29	2½	1.15	26	3	2.05
30	3	2.05	27	3	1.4
31	4	4.2	28	4	2.42
			32	4½	2.94
			33	4	2.46
8 Cases Avg.	3	1.83	10 Cases Avg.	3.3	2.74

permitted a more adequate packing of the uterus. The latter would seem to be true, for a slightly longer pack was used in the moist group than in the dry group.

We wondered regarding the effect of the moisture on the hemostatic action of the pack. No case of true atonic uteri with post-partum hemorrhage was encountered in this group. However, the moderate bleeding of the etherized nonstimulated (oxytocic) uterus was very adequately controlled; no difference could be noted in this regard in the two types of packs used.

Preservation.—In our earlier work, we prepared the packs as indicated and wrapped them in cloth for sterilization. This was not a permanent preparation, so we attempted to have available in the delivery room, dry sterile packs and sterile containers of sulfanilamide powder, thus permitting us to prepare the pack fresh as required. With

a frequently changing nursing and intern staff, much time was lost, which, in patients with hemorrhage might prove to be critical.

The experimental packs of this study were supplied to us in small glass jars with sealed and clamped tops. This preparation permitted the pack to remain moist for periods up to eight months after fabrication. The pack remained pliable and the sulfa was not precipitated out. On checkup, the 20 per cent gauze still contained approximately 1.5 Gm. per yard.

Summary

In both the present and previous study the morbidity, in terms of temperature elevation over 100.4° F. was surprisingly low. Fear of infection has frequently been responsible for undue delay in packing a bleeding, atonic uterus. With the great reduction in morbidity and infection resulting from the addition of sulfanilamide to the pack, its early use in the control of hemorrhage is to be recommended.

This study is a continuation of work on sulfanilamide impregnated gauze for uterine packs and reports on the physical features of such packs.

From these studies we believe a glycerin 20 per cent sulfanilamide gauze made up as a 2½-inch (16-fold) by 5-yard roll, prepared in a sealed glass container is the most satisfactory pack for intrauterine tamponade for use in the average hospital delivery room.

The experimental packs used in this study were prepared by the Johnson & Johnson Research Foundation, New Brunswick, N. J.

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ECLAMPSIA WITHOUT CONVULSIONS, HYPERTENSION OR COMA

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ECLAMPSIA without convulsions is rare. Slemons[2] reported 9 cases, the last two in 1907. Coffiere[3] reviewed the literature up to 1927 and found 38 cases. The last discussion of this condition appeared in 1933 by Arthur G. King[4] who reported the forty-fourth case. However, Dieckmann[1] mentions another case in his book *Toxemias of Pregnancy*. Other cases have undoubtedly been undiagnosed because of lack of necropsy evidence or have not been recorded in the literature.

Eclampsia without convulsions, or coma, is extremely rare. Wegner and Dieckmann reported the eighth such case in 1932. The diagnosis was made at autopsy which revealed the presence in the liver of periportal hemorrhages, anemic infarcts or thrombosis of the portal vein.

Cruichshank, Hewitt and Couper reported that 18 per cent of their eclamptic patients had blood pressures less than 141 mm. of Hg, while 22 per cent were over 200 mm. Hg, the mean being 168 mm. Hg. Hernson found that 95 per cent of his eclamptic patients had a systolic pressure over 136 mm. Hg.

Eighty-five per cent of eclamptic patients reveal edema of legs and almost 100 per cent have either latent or demonstrable edema.

The following is a report of eclampsia without convulsion, hypertension, edema or coma.

Mrs. L. G., a primigravida, aged 29 years, and at term November 22, 1943, presented herself for examination June 10, 1943. Her past history was irrelevant; blood pressure was 110/80, uterus size of 14 weeks' gestation; urine negative, weight 105 pounds.

The essential data of subsequent office visits are as follows:

	UTERUS	BLOOD PRESSURE	URINE	WEIGHT
7/8/43	18 weeks	112/80	negative	107¼
8/5/43	22 weeks	130/86	negative	108¾
9/2/43	26 weeks	136/84	negative	111½

On 9/16/43 her blood pressure was 145/90, uterus 28 weeks in size, weight 111½. Patient remarked she was emotionally disturbed due to her husband's eventual entrance into the Army. She was told to remain at bed rest and return in one week. On 9/23/43 she was feeling well again, her blood pressure being 140/88, and her weight 112½. The uterus seemed smaller (size of 26 weeks), but the fetal heart sounds were good. She was placed on a low protein, salt-free diet, and bed rest. One week later, 9/29/43, the uterus was the size of 26 weeks, blood pressure was 130/80, and the urine contained one-plus albumin. She was seen again on 10/13/43 with no subjective complaints. The uterus was now the size of 24 weeks' gestation, fetal heart sounds good, blood pressure 150/88, urine ++ albumin, and her weight was 114½ pounds. Patient was told to continue diet and bed rest and report in one week.

*Presented at a meeting of the Chicago Gynecological Society, December 17, 1943.

Four days later, on 10/17/43, at 12:30 P.M., the patient phoned and complained of mild epigastric distress. She was told to remain at bed rest and apply heat over the epigastrium. At 2:30 P.M. patient again phoned stating that the pain was more severe and associated with mild nausea. Paregoric was then prescribed. At 4:00 P.M. she again phoned and stated that pain was now very sharp and radiated to back and right shoulder and was associated with nausea and vomiting. She was seen at 4:30 by one of us, and found to be doubled up with pain, sharp in character, radiating to the back and right shoulder. She had emesis at this time and the vomitus contained bile. There was slight rigidity over the right upper quadrant associated with marked tenderness to pressure over the gall bladder area. Her pulse was 80, blood pressure was 128/86, no edema present and she was fully alert. A diagnosis of biliary colic was made and morphine sulfate gr. ¼ was administered. By 5:15, she was more comfortable. At 7:15, an urgent phone call was received stating that she had fainted and did not respond. The breathing was deep and stertorous. At 7:40 when one of us arrived at the home, death had just occurred. On questioning the attendants, it was learned that she suddenly did not respond to questioning, but no convulsions were noted at any time. An autopsy was performed on 10/18/43 by Dr. Otto Saphir, pathologist of Michael Reese Hospital, revealing the following essential findings:

"The liver is enlarged and presents a mottled appearance, the mottling being caused by large areas of hemorrhage which vary in size from one or two millimeters to a few centimeters in diameter. Many of the latter are fused by confluence. This is particularly marked in the region of the diaphragmatic surface of the right lobe. On section, similar areas are found on the cut surface. The interliver tissue shows distended central zones. Within the region of the hemorrhages the liver tissue is not recognizable, but appears to be necrotic. The gall bladder contains a small amount of thin liquid bile. The bile passages are patent. Neither the branches of the hepatic veins, which are carefully dissected, nor the branches of the portal vein show any noteworthy change.

The kidneys are of a greenish, grayish, brown color. The capsule scrapes away with ease, leaving a smooth surface. On section, the architecture of the cortex is somewhat obscured, but otherwise no changes are noted.

The vagina and cervix appear normal. The uterus corresponds to about seven months of pregnancy. When the uterus was opened, it was found that the fetal sac was devoid of any fluid. The placenta was firmly attached to the uterus and the membranes were also attached to the mucosa of the uterus. The fetus measures 35 cm. in length. No changes in the organs examined were noted, externally and internally.

Microscopic Findings.—

Liver: There are large areas of hemorrhages which are invaded by many polymorphonuclear leucocytes. There is a considerable necrosis seen in these regions. These areas are situated predominantly in the regions of the periportal spaces while often the central zones show no changes with the exception of a moderate cloudy swelling of the lining cells. Often a small bile duct is noted practically completed, surrounded by an area of necrosis, with red blood corpuscles and a few polymorphonuclear leucocyes. Though blood vessels cannot be defi-

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Fig. 1.—Eclamptic liver: Note the enlargement due to the presence of subcapsular hemorrhages, most pronounced along entire diaphragmatic surface.

nitely identified in the necrotic regions, it seems that some of the larger veins are involved. They show evidence of necrosis in at least some portions of their walls.

The outstanding changes in the kidney are a rather severe cloudy swelling involving the lining cells of the convoluted tubules, and also a number of lining cells of connecting tubules. The lumina of the latter contain much of a reddish, granular material. The glomeruli show no changes with hematoxylin-eosin stain. However, a MacGregor preparation reveals that the basal membranes are distinctly thicker than normal and sometimes appear smudgy. A number of arterioles show no changes. An occasional small blood vessel—it cannot be decided whether this is a vein or not—shows necrotic walls. Here and there the Goormaghtigh (justoglomerular) apparatus is recognized but no changes are elicited.

The uterus shows typical changes of pregnancy. The placenta shows several large infarcts, the villi perhaps slightly smaller than normal, but all of them show open blood vessels.

Pathological Diagnosis.—

1. Eclamptic liver
   Cloudy swelling of the myocardium and kidneys
   Petechial hemorrhages in the endocardium
   Pregnant uterus with about 7-month-old fetus
   Absence of amniotic fluid
   Edema of lungs.

In conclusion, the case is both rare and interesting because of the following:

1. It demonstrates eclampsia without convulsions, and questionable coma.
2. A normal blood pressure was associated with the eclampsia while prior to the episode there was a slight to moderate hypertension.
3. The absence of visual and latent edema in the presence of eclampsia
4. The possible relationship between absence of amniotic fluid to the above toxemia.
5. Acute involvement of liver with little or no involvement of kidneys and other organs.

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REPORT OF 67 CONSECUTIVE POST-PARTUM STERILIZATIONS

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SINCE 1940, sixty-seven post-partum sterilizations have been done at the Louisville General Hospital. The Madlener technique with some minor modifications has been employed. Not included in this series are twenty-four Madlener sterilizations done at the time of cesarean section. Sixty-three cases were sterilized within twenty-four hours, two cases after twenty-nine hours, one case thirty-one hours after delivery, and one was done on the tenth post-partum day.

In this series we have fifty-three cases that were delivered spontaneously, two that were delivered spontaneously with an episiotomy, three delivered by low forceps, three delivered by episiotomy and low forceps, five by breech extraction, and one by podalic version. There were four sets of twins.

In this paper we are reporting the use of local anesthesia, a transverse incision, the crushing of the Fallopian tubes close to the cornu of the uterus, and a silk-suture closure of the abdominal wall. We are also presenting additional evidence that post-partum sterilizations do not cause an increase in puerperal morbidity if done within twenty-four hours after delivery.

Technique

The present policy of the department does not allow a sterilization to be performed if the patient is more than twenty-four hours post partum.

We are employing local anesthesia using 150 to 200 c.c. of 0.5 per cent novocain with 0.2 c.c. of adrenalin per 100 c.c. of novocain. Two hours before operation, the patient is given three grains of nembutal, and morphine and scopolamine are given twenty minutes preoperatively. Adair and Brown[1] report the use of local anesthesia, and we have also found this method adequate and comfortable for the patient.

Except for a few modifications, we use the same technique as followed by Adair and Brown.[1] Instead of a longitudinal incision, we have been using a 2 to 2½ inch transverse incision of the skin and anterior sheath of the rectus. The muscle itself is retracted and very often the diastasis recti affords easy retraction. The posterior sheath and peritoneum are incised transversely in turn. The incision is made over the fundus of the uterus. We believe that this facilitates seizure of the Fallopian tubes with a Babcock clamp. After we identify the tube by tracing it to its fimbriated end, it is crushed in two places by a single application of a Kelly clamp. One of these crushed areas is always two centimeters from the cornu of the uterus. We crush the tubes close to the cornu in order to prevent conception through accessory ostia. For the double ligation we use heavy braided silk. In all our recent cases, silk has been used to close the abdominal wall.

In this series there were thirty-four transverse incisions, most of which were done in the last two years. A silk closure was used on thirty-nine cases. None of our wounds have been infected.

Indications

The decision for sterilization of all but the mental cases rests with the department of obstetrics and gynecology. All mental cases have to be passed by the department of psychiatry. The following chart shows the indications for sterilization in this series:

Toxemia	
All types of recurrent toxemia	22
Heart Disease	
Hypertensive cardiovascular	8
Rheumatic	2
Mental Disease	
Feeble-minded	8
Schizophrenia	2
Manic depressive	2
Orthopedic	
Ankylosis of left hip and knee	1
Midthigh amputation	1
Lung Disease	
Moderately advanced tuberculosis	1
Far advanced tuberculosis	1
Tuberculous effusion	1
Metabolic Disease	
Diabetes	2
Varicosities	
Varicose veins of legs and vulva	2
Renal Disease	
Bilateral hydronephrosis	1
Recurrent pyelitis	1
Nephrosis	1
Miscellaneous	
Phlegmasia alba dolens	1
C.N.S. (syphilis)	1
Pelvic disproportion with previous section	1
Multiparity	8
Total	67

Post-partum Interval

Of the sixty-three cases done within twenty-four hours, the longest interval was twenty-two hours and the shortest interval was one hour. Sixteen cases were done in five hours or less. Twenty cases were sterilized between five and twelve hours. Twenty-six patients were sterilized between twelve and twenty-four hours. Two cases were sterilized after twenty-nine hours, and one case was done after thirty-one hours. One case was sterilized on the tenth post-partum day. The average interval for sixty-three cases done within twenty-four hours was 11.4 hours. For all cases exclusive of the case done on the tenth day, the average interval was 12.3 hours.

Morbidity

Our percentage morbidity was 2.9 per cent or two cases. This compares with the morbidity reports of Adair and Brown,[1] Hewitt and Whitley,[4] Birch,[7] and Lock, Forman and Webster.[5] There were no mortalities. Herewith is a review of the two morbid cases.

CASE 1.—(7802.) Gravida xv, para xiv. The post-partum interval was twelve hours following a spontaneous delivery of twins. At the time of operation the surgeon discovered many adhesions between the omentum and peritoneum. In order to reach the tubes, he found it necessary to incise an avascular portion of the omentum. He later repaired the omentum with chromic catgut. The abdomen was closed with catgut. This patient was classified as morbid for she had a temperature of 100.4° F. on her seventh postoperative day, and 100.6° F. on her eighth postoperative day. No cause for the fever was ascertained.

CASE 2.—(70751.) Gravida i, para 0. This patient was delivered spontaneously following an episiotomy. The post-partum interval was ten hours. Her prenatal record showed that she was treated for a mild pyelitis during her twentieth week of pregnancy. This patient arrived in the operating room with a temperature of 100.4° F. After the abdomen was opened a full bladder was found, and the operator decided that the patient had to be catheterized before he could resume the procedure. On the third day, the patient had a temperature of 101° F., and complained of her episiotomy hurting. On the fourth day the temperature was 101.2° F., but a catheterized urine specimen showed no findings consistent with a urinary tract infection. She had no subjective symptoms of pyelitis. At no time was her episiotomy broken down or infected. The patient was started on sulfathiazole on her fifth day and was completely afebrile on her eleventh.

Postoperative Stay

The average postoperative stay was 10.2 days for sixty-five cases. One patient stayed on for treatment of her diabetes, and another was retained by the department of psychiatry. Forty-two cases left the hospital on their tenth day or less. Up until last year most patients stayed 10 to 12 days. Now they are discharged on their ninth or tenth postoperative day.

Summary

Sixty-seven consecutive cases of post-partum sterilizations have been reviewed. With some minor changes, the Madlener technique as reported by Adair and Brown[1] has been used. The usage of local anesthesia, a transverse incision and crushing of the tube two centimeters from the cornu uteri is recommended. We believe that this is a safe procedure if done within twenty-four hours after delivery. Notwithstanding the fact we have reported fourteen cases that have had some obstetric intervention, we believe that there will be little risk with cases that deliver spontaneously. The operative procedure does not prolong the hospital stay beyond the regular post-partum stay, nor is there any increase in the puerperal morbidity.

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BRENNER TUMOR OF THE OVARY ASSOCIATED WITH SARCOMATOUS CHANGE IN FIBROMYOMATA UTERI

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THE perplexing problem that is involved in the classification of ovarian tumors is almost overwhelming when one glances at the outline that was offered some 15 years ago. Now, thanks to the continued study by pathologists and constant reporting of cases in the literature by clinicians, a clearer understanding is gradually evolving. It is with this in mind that we present this case report, hoping it may in some way contribute further evidence.

In 1907, Brenner[1] first described the type of tumor we are presenting but called it oöphoroma folliculare. He made no differentiation from the granulosa cell growths and it was not until 1932 that Robert Meyer[2] sharply distinguished between the two. Since then various authors, Novak, von Szathmáry and Varangot, have reported groups of cases and reviewed the literature. The total number of cases now approaches 130.

The case we offer is quite typical both clinically and pathologically and is unusual only in that it is associated with a fibromyoma of the uterus which showed sarcomatous degeneration. The symptoms which eventually drove the patient to her physician were excited by the tumor making contact with the cecum and the bleeding caused by the fibromyoma. How long the Brenner tumor had existed, or how long it would have persisted had some adjacent structure not become involved, cannot be answered.

Case Report

Mrs. W. A. R., 51 years old, was first seen on December 7, 1942, at which time she complained of the following: (1) R.L.Q. pain and tenderness, which at times was excruciating but did not cause nausea or vomiting—four weeks' duration. (2) Loss of ten pounds in weight. (3) A daily temperature elevation between 99 and 100 degrees F. of two weeks' duration. (4) Vaginal bleeding requiring one or two pads daily, of seven months' duration.

Her menses first began at the age of 12, were regular every 28 days, lasted 4 to 5 days and were always associated with pain on the first day. In 1940, her periods became irregular and the amount of bleeding was variable. Hot flashes were intense. Periods ceased in November, 1941, and she had no discharge or flow until April, 1942, when the present illness began.

Her only pregnancy occurred at the age of 25, and terminated in a 2½ months' complete abortion. She gave a history of having been treated for arthritis in the left hand in 1931. Had pneumonia in 1936 and afterward, received treatment for hypertension and bradycardia.

Physical examination revealed a white, short, obese, pale female. T. 99.6° F., P. 90, B.P. 140/90. Lungs were clear. Heart tones were of

good quality and rate was regular. The abdomen was thick walled and tender in the entire lower portion but particularly on the right side where a mass was questionably outlined. The vaginal outlet was marital and cervix normal. The uterus was tender, irregular and enlarged upward and laterally toward the cecum. Bimanual examination was not entirely satisfactory because of the obesity and tenderness. A probe showed the uterine canal to be 3½ inches in length and somewhat irregular. This maneuver caused an increase in the bleeding.

Provisional Diagnosis.—Large fibromyoma of the uterus with degeneration and possible early carcinoma of the fundus.

The patient was referred to the hospital December 10, 1942. X-ray examination of heart and lungs was essentially negative except for elevation of the right side of the diaphragm. X-ray study of the gastrointestinal tract was interpreted as follows: "Mass lesion of the pelvis causing deformity of the cecum from extrinsic pressure; displacement of the sigmoid due to same; displacement of the small intestine from the pelvis."

Laboratory Report: R.B.C. 4,640,000. W.B.C. 11,650. Hemoglobin 86 per cent. Two urinalyses were normal.

Operation was performed on December 15, 1942. Curettage revealed no endometrial tissue. The abdomen was opened by a right paramedian incision, revealing a large ovoid-shaped ovarian cyst. Its origin was from the left adnexa and its right pole was adherent to the cecum by fibrin and fibrinous bands. The cyst was easily freed from the bowel and was found definitely to be of solid structure at the point of contact. This was the portion which showed the Brenner tumor.

The tumor and left tube were removed and a panhysterectomy and right salpingo-oophorectomy were performed. The uterus showed a 4 to 5 cm. fibroid at left cornu. There was no evidence of invasion or glandular enlargement.

The postoperative course was normal, the patient being discharged on December 29, 1942.

Pathologic Examination.—The left ovarian tumor is 13 cm. in diameter. In one pole there is a solid area 5 cm. in diameter. From the inner surface of this solid portion there is a soft, papillary mass projecting into a cyst, the latter being 8 cm. in diameter. The solid area cuts with increased resistance and the cut surface shows small cysts and an occasional area of hemorrhage.

Sections from the solid portion show numerous nests of typical Brenner cells. Where well preserved, the tumor cells are polyhedral, flat and arranged in circumscribed or elongated masses. In all cases the tumor cells are surrounded with dense fibrous tissue. Many of the tumor nests show degenerative changes and are lined with a single layer of cuboidal or flat cells. Frequently epithelial remnants are seen in the center of these degenerated nests.

Sections from areas adjacent to the papillary growth show more extensive degeneration of the Brenner tumor nests. Here there is a greater tendency to elongation and the lining cells become more columnar. In the fully developed, pseudomucinous area, the tumor cells surround papillary strands of vascularized connective tissue stroma. The cells become more cylindrical and are usually one layer in thickness. Cilia were not noted in either the pseudomucinous structure, or solid area. Many Brenner tumor-cell nests are present in the stroma of the pseudomucinous growth.

Sections of the soft Leiomyoma in the uterus show it to be very cellular. The tumor cells are atypical, variable in size and both round and spindly in shape. Mitotic figures are fairly numerous.

Follow-up.—The patient was last seen on March 5, 1944. She was feeling well. Hot flashes were controlled by Premarin. Abdominal wound and vault were well healed. There was only slight pelvic tenderness and no masses.

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SPONTANEOUS POST-PARTUM DISAPPEARANCE OF MASSIVE CONDYLOMATA ACUMINATA OF THE VULVA

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CONDYLOMATA acuminata of the perineum, vulva, vagina and cervix are seen not infrequently among those pregnant women with a profuse vaginal discharge. Recently radium[1] has been used to treat small warts of the vulva soon after delivery.

The object is reporting this case is to re-emphasize the possibility of complete spontaneous disappearance of massive condylomata acuminata of the vulva after delivery.

The patient, a 23-year-old gravida iii, para ii, entered the San Francisco City and County Hospital Prenatal Clinic March 24, 1942. Her last menstrual period was December 23, 1941, and the expected date of confinement was September 30, 1942. Her course was uneventful until July 21, 1942, when she presented herself at the clinic with the complaint of itching warts of the vulva for several weeks. On examination, the major and minor labia were found to be covered with multiple minute papillomata and there was a 1-centimeter condyloma at the fourchette (Fig. 1). She was sent into the hospital where under caudal-block anesthesia with 40 cubic centimeters of 1 per cent procaine hydrochloride, the growth was excised from the fourchette and the remainder of the warts were removed and the bases cauterized with the actual cautery. Petroleum jelly was applied to the cauterized areas.

The patient failed to report again to the clinic for examination until 3 weeks before confinement. At that time, there was a 6-centimeter warty growth involving both minor labia. Only a minute recurrence was present at the fourchette. Because of the closeness to term, it was considered inadvisable to exercise or cauterize the tumor. The patient was told to wash the area several times each day with plain water and to keep the growth thoroughly dried at all other times. She re-entered the hospital October 2, 1942, and delivered spontaneously after a 2-hour labor assisted only by a right medio-lateral episiotomy. The labial growth did not interfere with the delivery and there was no bleeding from it.

The post-partum course was afebrile and the patient was dismissed on the tenth day with the advice that she keep the vulva clean and dry. It was planned to wait several weeks before instituting any specific treatment to eradicate the growth. The warts rapidly diminished in size until 8 weeks post partum, at which time there remained only a 3-millimeter nodule just below the fourchette and a 1-centimeter group of nodules on the lateral surface of the right minor labium. Still without any therapy other than cleanliness and dryness, the warts completely disappeared by January 9, 1943, 14 weeks post partum.

The Wassermann reaction was negative and smears taken from the urethra and cervix were negative for gram-negative diplococci. No *Trichomonas vaginalis* were found. A few mycelia were present at the first examination of the vaginal discharge, but none were found thereafter.

Conclusions

During the first two trimesters of pregnancy, condylomata acuminata of the vulva, vagina and cervix should be treated by excision and cauterization. Recurrences frequently occur and can be effectively con-

trolled by frequent cauterizations, coupled with measures to decrease the discharge which is usually present.

The problem in the latter part of the third trimester, must be approached in a different manner. Because of the imminence of labor and the increased vascularity of the tissues and the tumor, excision or

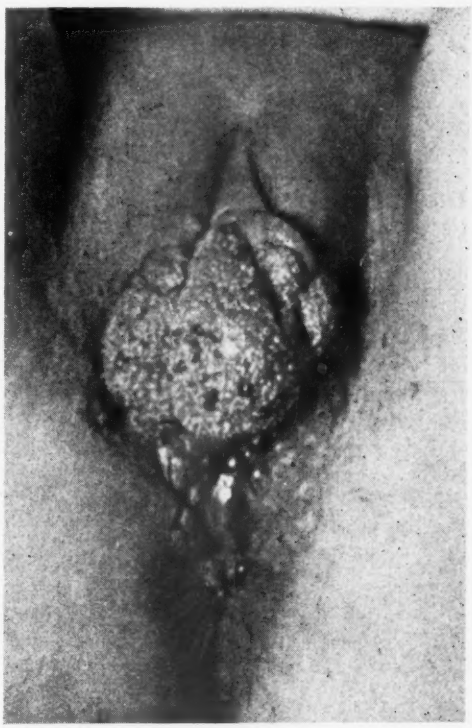

Fig. 1.—Pregnancy at 7 months. Multiple small condylomata acuminata of the major and minor labia and a 1-centimeter papilloma at the fourchette.

cauterization is inadvisable. In addition, there is always a possibility of increasing the chances of infection. Under these circumstances, I consider it preferable to take measures to control the discharge from the vagina and the infection of the tumor, and to deliver the patient by the most appropriate means. If the infection has been effectively checked and the tumor does not, as in the present case, offer an obstruction to delivery, she should be delivered from below. However, should the tumor be large and ulcerated, or involving the perineum to an appreciable extent, then extraperitoneal cesarean section has to be considered seriously as offering the lesser hazard to the patient.

After delivery the major hazard to the patient has passed, and she may be observed for a period of weeks during which time cleanliness is stressed. Radium, x-ray, cauterization or excision should be reserved for those cases that show no evidence of regression after 3 to 4 weeks.

Before attempting to evaluate the efficacy of any method of treating these lesions, cognizance must be taken of the fact that spontaneous disappearance of condylomata acuminata does occur after delivery.

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PRIMARY OVARIAN PREGNANCY

Report of Three Cases

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IN THE past 24 years there have been 206 cases of ectopic pregnancy at this hospital. Primary ovarian pregnancy has occurred in three instances of this series. These will be described below. Mercer,[1] in 1614, suggested that such an occurrence was possible and since that time there have been approximately 120 cases reported in the literature. However, an authentic case must fulfill the widely quoted criteria proposed by Spiegelberger. These are: 1. An intact and normal uterine tube of that side. 2. Connection of the pregnancy mass to the uterus by the uteroovarian ligament. 3. That the gestation sac occupy the position of the ovary. 4. That there be unquestionable ovarian tissue in the wall of the sac. According to Meyer and Wynne,[2] the first authentic cases are those of Kauwer in 1897 and Tussenbroeck in 1899. Thomas,[3] in June, 1943, set the number of authentic cases at 65.

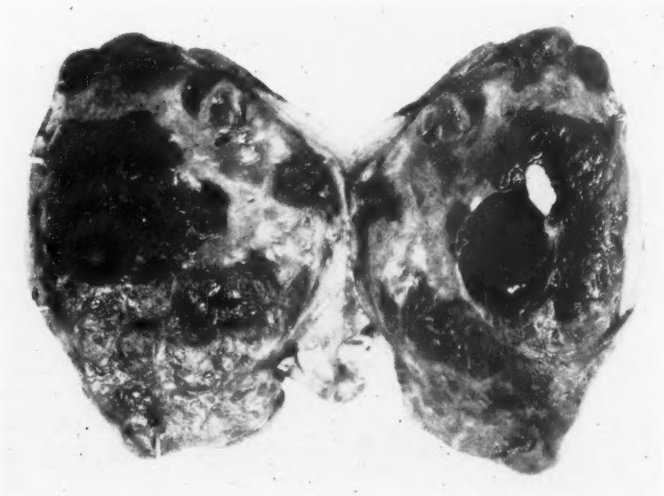

Fig. 1.—(Case 1.) Gross specimen on hemisection. Note centrally located gestation sac, embryo and deeply hemorrhagic ovary. Between the two halves of the ovary is the stump of the uteroovarian ligament. (×1.2.)

CASE 1.—(Service of Dr. O. R. Lillie.)

E. V., a white female, 20 years of age, married, gravida 0, admitted to the hospital January 8, 1944 because of pain in the right lower quadrant. The pain began one week prior to the admission. In November, 1943, the patient had her last normal menstrual period. Subsequently irregular episodes of bleeding persisted for three weeks. On admission, physical examination was negative except for tenderness in the right lower quadrant and a palpable mass in the right adnexal region. In the early part of January, 1944, the Friedman test was posi-

tive. At laparotomy, the internal genitalia, with the exception of the right ovary, were found to be normal. Both uterine tubes were without gross change. The right ovary, which was in its normal position and attached to the uterus by the uteroovarian ligament, measured 6 by 4 by 4 cm. On section of the ovarian mass, there was encountered a centrally located 22 mm. cavity filled with a clear, watery fluid. A well-developed 8 mm. embryo was attached to the wall of this cavity. The head and eyes, the cardiac protuberance, and the limb buds of the embryo were clearly visible (Fig. 1). The major share of the ovarian substance around the gestation sac was deeply hemorrhagic. Microscopic examination of the hemorrhagic ovarian tissue revealed the presence of chorionic villi. No decidual tissue was found in the sections of the ovary.

Case 2.—(Service of Dr. A. H. Lahmann.)

H. H., a 24-year-old white, married female, gravida 0, admitted to the hospital July 21, 1941 because of bleeding for four days prior to entrance. The last normal menstrual period occurred on May 17, 1941. The patient was a known cardiac invalid with a severe rheumatic mitral stenosis. Pelvic examination revealed a mass in the right adnexa. The Friedman test at this time was positive. Dilatation and curettage was performed and a microscopic diagnosis of "decidual tissue" was made. Five days later, a right salpingo-oophorectomy was performed. The specimen measured 7 by 5 by 3 cm. and weighed 50 grams. The tube was average in size and upon opening was found to be entirely normal. The ovarian mass revealed a centrally located 10 mm. sac outlined by a smooth, glistening membrane and surrounded by deeply hemorrhagic tissue. The uteroovarian ligament was attached to the specimen of ovary.

Microscopic examination of the ovarian tissue revealed the presence of chorionic villi and decidual cells. No embryo was found in this case.

Case 3.—(Service of Dr. R. S. Cron.)

W. M., a 23-year-old married, white female, gravida 0, admitted to the hospital May 16, 1940 because of nausea, vomiting and vaginal bleeding appearing on the day of admission. One and one-half months prior to admission, the patient experienced pain in the lower part of the abdomen, and irregular vaginal bleeding. A Friedman test done at that time was positive. Corpus luteum extract was administered and the patient was confined to bed for one month.

In four years of married life she had not conceived. One year previously, a complete study was performed because of sterility. Menstrual history, however, was regular.

Physical examination was essentially negative except for tenderness in the left lower quadrant and a palpable mass in the left adnexal region. At laparotomy a large mass was found occupying the position of the left ovary. This was attached to the uterus by the uteroovarian ligament. The left uterine tube was not removed and was described as normal. The ovarian specimen measured 8 by 7 by 4 cm. One part of the specimen was occupied by a clear serous cyst measuring 4.5 cm. in diameter; the balance was made up of coagulated blood measuring 5 cm. No sac or embryo was found in this specimen. Microscopic examination of the ovarian substance and coagulated blood showed the presence of a corpus luteum and chorionic villi. Other findings at the time of surgery revealed a corpus hemorrhagicum of the right ovary and endometrial transplants in the posterior cul-de-sac.

Comment

The mechanism by which the ovary comes to bear the dividing and developing ovum is a matter of speculation. The most probable theory is that of fertilization of the normal ovum within its follicle. Spermatozoa may reach the surface of the ovary and fertilize an ovum within a recently ruptured Graafian follicle. Sterilitiy is a rather common factor in the cases of the ovarian pregnancy. The three cases reported herein had not been gravid prior to the occurrence of ovarian pregnancy. Wollner,[4] also stresses the factor of previous sterility and suggests that there may be some inherent defect in ovulation. On the other hand, Curtis[5] believes that it is possible for a normally fertilized ovum (in the tube) to lose its "traction" and slide back into a recently ruptured Graafian follicle wherein nidation may take place. Finally, nidation may take place in other epithelial structures such as endometrial implants or Müllerian duct remnants on the surface of the ovary. Cron[6] has noted a case of ectopic pregnancy in an endometrial implant on the surface of the rectum. It is his opinion that in Case 3, the ovarian pregnancy developed in an area of endometriosis.

Summary

Three cases of primary ovarian pregnancy are presented. All are authentic according to the classification of Spiegelberg. Pregnancy had not occurred in these individuals prior to the development of ovarian gestation. Fertilization of the ovum within its follicle is the probable mechanism in Cases 1 and 2. In the third case, pregnancy evidently had taken place on the surface of the ovary in an endometrial implant.

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THECOMA OF THE OVARY WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME)

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ALTHOUGH fibroma of the ovary associated with ascites and hydrothorax was reported as early as 1879 by Cullingworth,[1] it was not until 1937 that the condition was recognized as a clinical entity when it was described by Meigs and Cass.[2] The syndrome is not common; only 30 cases had been recorded by January 1943, according to Meigs and his associates,[2] who collected the cases reported in the literature. There have been patients undoubtedly, exhibiting this symptom complex who were considered to have inoperable malignancies, and who were treated only palliatively. The condition can be cured only by surgical removal of the tumor. Therefore, it is important to familiarize the medical profession with this syndrome so that they may consider it in the differential diagnosis when a patient is seen with fluid in the abdomen and chest, and institute surgical treatment as soon as the condition is recognized.

The mechanism of formation of ascites and pleural effusion associated with ovarian tumors remains speculative. It has been ascribed to the "shocking" action of the tumor, torsion of the pedicles of the tumor, the presence of pleuroperitoneal tubes and to penetration via the diaphragmatic lymphatics.[1]

Although this syndrome may appear at any age, most of the reported cases have occurred following the menopause. The clinical picture is not characteristic and often simulates a pelvic malignancy with metastases. The symptoms may be referable primarily to the presence of fluid in the chest, or they may be only suggestive of the pelvic mass. The patient may complain of gastrointestinal disturbances such as cachexia and loss of weight, and of dyspnea, abnormal vaginal bleeding, and menstrual difficulties.

The rarity of Meigs' syndrome would appear to justify the report of another case. Whereas most of the reported cases have been fibromas, this is a case of thecoma of the ovary associated with ascites and hydrothorax. Since the patient was under observation before any evidence of ascites and hydrothorax appeared, this case demonstrates how rapidly fluid may accumulate in the peritoneal and pleural space, a point which Meigs had emphasized.

Miss O. W., white, aged 44, came to the clinic April 30, 1942 with a complaint of leucorrhea. Vaginal examination revealed a hard, apparently fixed mass which was attached to the posterior surface of the uterus on the left. A small cervical polyp was cauterized, following which the leucorrheal discharge disappeared.

On June 25, 1943, fourteen months after the patient was first seen, she returned because of abdominal distention and pain. She had not menstruated for six or eight months, but had not noted any pronounced menopausal symptoms.

Abdominal palpation revealed a gaseous distention and pain on manipulation. On vaginal examination, a mass the size of an orange was felt in the pelvis. The mass could not be lifted out and was somewhat sensitive on manipulation.

Roentgenograms of the chest on June 29, 1943, revealed haziness in the right base which was interpreted as due to a thickened pleura.

It was considered advisable to observe the patient for a while. She returned ten days later at which time the mass had definitely increased in size and its removal was advised.

The patient was admitted to Touro Infirmary July 6, 1943. For one week before entrance to the hospital, she had had diarrhea. She also complained of a feeling of tightness in the abdomen and severe backache. For several days before admission, she could hear splashing noises in her abdomen when she moved. For four days prior to admission, she had a slight nonproductive cough and slight dyspnea with a sense of fullness in her chest.

Examination of the chest revealed flatness to the level of the eighth rib over the right base. No breath sounds could be heard and tactile fremitus was absent. Immediately above this area, fine crepitant râles could be heard. The heart appeared to be slightly enlarged to the left with a normal rate and no murmurs. The abdomen was protuberant and symmetrically enlarged. The skin was tense. Percussion revealed dullness and flatness in the dependent portions of the abdomen. Shifting dullness and a fluid wave were demonstrated. No masses could be felt. The liver and spleen were not palpable. The only significant finding on vaginal examination was a mass in the left adnexal region which was interpreted as an ovarian tumor.

On July 7, 1943, under a general anesthetic, a laparotomy was performed. Approximately one gallon of amber colored fluid was found in the peritoneal cavity. Exploration of the pelvis revealed a solid tumor of the left ovary, which was attached to the posterior peritoneum, filling the cul-de-sac and the posterior surface of the broad ligament. A small fibroid was felt in the uterus. A bilateral salpingo-oophorectomy and total hysterectomy were performed.

The pathologic report showed a tumor of the left ovary measuring 12 cm. by 7 cm. by 7 cm. The external surface was covered by a firm membrane and was grayish-white in color except for several areas of golden yellow. Section revealed a cut surface which varied in color from light reddish-brown to golden yellow. The golden-yellow color was intermingled in island-like formations within the general surface which appeared to be from grayish-white to light reddish brown. The tumor was fairly firm in consistency but showed several local areas which were soft and were golden-yellow in color. The uterus and cervix measured 6 cm. by 3½ cm. by 2½ cm. The endometrial cavity was normal in contour. The myometrial wall revealed several intramural leiomyomas. The cervix contained an endocervical polyp measuring 2 cm. by 4 cm. by 1 cm. The tubes were densely adherent to the ovaries and the fibrinated ends were not patent. The right ovary revealed a ruptured follicular cyst on one pole.

The microscopic diagnoses were thecoma of the ovary, follicular cysts of the ovary, chronic salpingitis, intramural leiomyomas, chronic cervicitis and endocervicitis and benign endocervical polyp.

The patient's convalescence was uneventful. Examination of the chest on July 12, 1943, revealed a Gracca's triangle at the right base extending to the sixth dorsal vertebra. No fluid was demonstrable in the abdomen. By July 15, 1943, evidence of pleural fluid was almost gone; there was a suggestion of a small amount of fluid at the right base posteriorly near the mediastinum. The breath sounds were diminished and tactile fremitus decreased over the right base.

Follow-Up Examination.—On July 30, 1943, a small amount of fluid was noted in the right base of the thorax. On August 23, 1943, pelvic examination was negative. No fluid was found in the abdomen. The patient had no complaints and was discharged. On March 1, 1944, when the patient was last seen, she had no complaints.

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Department of Statistics

CESAREAN SECTION AT THE BRONX HOSPITAL*

(An Analysis of 494 Operations in 20,763 Deliveries)

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THE report of the Committee on Maternal Mortality[1] which was presented at the Academy of Medicine some years ago, cited numerous instances of cesarean operations which were done by surgeons, dermatologists, nose and throat specialists, and orthopedists. The incidence of the operation was high and the mortality was great. Some time later, from the Hospital Information Bureau,[2] figures were obtained from five standard and well-known hospitals where the incidence of the cesarean operation varied from one in eleven to one in twenty-four.

Because of the high incidence of the operation and the high mortality, a method was initiated at The Bronx Hospital in an attempt to keep down the number of the cesarean operations. Of course, it was realized that in the case of the private patient, her physician might resort to any procedure that he wished; nevertheless, it was felt that the hospital where the patient was treated has certain responsibilities in regard to the operations performed and must exercise a certain degree of supervision.

The practice then was instituted that the cesarean operation could only be done by the attending and associate obstetricians and gynecologists, and a few other men who were approved by the medical board. Except in the case where the operation was done by the attending physicians, consent had to be obtained before the performance of the section. This approval implied consultation which did not need to be direct. In addition, in cases of cephalopelvic disproportion and contracted pelvis, an x-ray examination was required before the operation. It is needless to say, that in the face of an emergency, such as, hemorrhage from placenta previa, or premature separation of the placenta, telephone permission could be granted.

With these considerations in mind, we have analyzed the figures for the past 10½ years, namely from July, 1932, through December, 1942, at the Bronx Hospital. There were 494 cesarean operations among 20,763 cases. This represents an incidence of one in forty-two or 2.4 per cent. Four hundred and twenty operations were done among 14,977 private patients, or an incidence of one in thirty-six, while on the ward service, there were 74 operations in 5,786 cases, an incidence of one in seventy-eight. This is shown in Table I.

*Read in part, by invitation, at The Bronx Gynecological and Obstetrical Society in May, 1943. Presented at the Section of Obstetrics, New York Academy of Medicine, December 28, 1943.

TABLE I. INCIDENCE

	NO. OF DELIVERIES	NO. OF CESAREANS	INCIDENCE—1 IN
Total	20,763	494	42
Private	14,977	420	36
Ward	5,776	74	78

The type of operations are shown in Table II.

TABLE II. TYPE OF OPERATION

TYPE	TOTAL
Classical	255
Two flap	215
Latzko	13
Waters	1
Porro	9
Abdominal pregnancy	1

It is to be noted that in more than half of the cases the classical type of operation was done.

An analysis of the indications for which the cesarean operation was performed is of interest. This is shown in Table III.

TABLE III. INDICATIONS

INDICATION	NO. OF CASES
Contracted pelvis	163
Cephalopelvic disproportion	93
Previous section	89
Placenta previa	67
Premature separation	29
Malpresentation	8
Cardiac, elective	5
Toxemias	7
Stenosis of the vagina	2
Previous gynecologic operations	6
Fibroids complicating pregnancy	9
Postmaturity	1
Abdominal pregnancy	1
Fetal distress	3
Elderly primigravidas	11

It is seen from this Table that in 256 cases, or more than half, the operation was resorted to because of a large baby or small pelvis. It will also be noted that in almost 20 per cent of the patients, the operation was performed because of the previous cesarean. A certain number of these were cases of contracted pelvis or cephalopelvic disproportion, but some represent instances where the original operation had been performed for incidents of pregnancy or accidents of labor. In this connection, reference might be made to recent articles which emphasize the fact that a vaginal delivery may be achieved in cases where the cesarean operation had been resorted to in a preceding pregnancy. In McLane's[3] figures from the Johns Hopkins Hospital and those of Kuder[4] from the New York Lying-in Hospital, more than one-third of the former cesarean cases were delivered per vaginam. Interestingly enough, too, from these articles it is seen that the babies born by the vaginal route were occa-

sionally larger than those born by the cesarean operation, even in cases of contracted pelvis. In addition, there were many cases where evidence indicated that healing had occurred by secondary intention in the course of the previous cesarean section. These studies would indicate that the fact that a cesarean had been performed at one time does not preclude the possibility of a vaginal delivery in a subsequent pregnancy, but the fear of a rupture of the uterus must be kept constantly in mind, and the patients watched with utmost care during their pregnancy and labor.

During the period under discussion, there were 17 deaths among the cesarean cases. This represents a mortality of 3.2 per cent. For the same period under consideration there were 45 obstetric deaths among the 20,763 patients. It can thus be readily seen that more than one-third (i.e. 38 per cent) of the maternal deaths was in cases where the cesarean operation was performed.

An analysis of these deaths (Table IV) shows that ten were among the classical and five among the two flap type.

TABLE IV. MORTALITY

HOSP. NO.	GRAVIDA	TYPE OF SECTION	INDICATION FOR SECTION	CAUSE OF DEATH
35052	1	Classical	Central placenta previa	? Peritonitis
42845	1	Classical	Funnel pelvis	Peritonitis
61835	1	Classical	Chronic nephritis	Postoperative shock
67950	1	Classical	Cervical malformation	? Peritonitis
67639	1	Classical	Placenta previa	Peritonitis
75232	1	Classical	Rheumatic heart disease	Cardiac failure
80068	1	Classical	Rheumatic heart disease	Cardiac failure
126307	1	Classical	Cardiac	Pneumonia
138918	1	Classical	Contracted pelvis	? Peritonitis
117256	1	Classical	Fibroid in lower canal	? Peritonitis
434145	1	Two flap	Contracted pelvis	Strep. sepsis
47503	1	Two flap	Flat pelvis	Pneumonia
124419	1	Two flap	Elderly primiparas	Shock and collapse
109700	1	Two flap	Contracted pelvis	Peritonitis
124867	11	Two flap	Previous section for flat pelvis	Pulmonary embolism
40100	1	Porro	Central placenta previa	Peritonitis
44529	1	Porro	Intrapartum sepsis	Peritonitis

Nine patients died of peritonitis and one of sepsis. That is, more than one-half of the deaths were due to infection.

It is interesting here to consider the mortality of the babies. Among the newborn infants, the death rate was 36 in 496 children (two sets of twins), or 8 per cent. Among these there were 16 cases of "ablatio" and 16 premature infants where the operation was done for placenta previa. In both of these indications, the fetus was already dead when the section was done.

As some basis for comparison, the report of DeNormandie[5] is of value. He gives an analysis of probably the greatest number of cesarean sections that have been collected and reported at one time. He reports on 11,030 cesarean sections in 333,731 deliveries; an incidence of 3.3 per cent. The low cervical operation was done in 53 per cent of the cases while the classical type was done in 42 per cent. Previous section as an indication was present in 29 per cent of the cases. The maternal mortality was 2.5 per cent with sepsis as the cause of death in 39 per cent. The fetal mortality was 9 per cent.

Summary

The cesarean operation is not to be regarded as a panacea for all types of labor and while the operation itself may be simple, it has a real mortality both for the baby and the mother. These must be considered before subjecting any woman to such form of interference.

Conclusion

The striking features of this report from The Bronx Hospital are first, the high maternal and fetal mortality, and secondly, the low incidence of the operation. We feel that the incidence of cesarean sections can still further be reduced. In the case of the elderly primigravida, there should be another indication other than age alone, that is, size of baby, the presentation and the type of pelvis should enter into the consideration.[6] Also, in the cases of former cesarean sections, the obstetrician may have the courage to permit vaginal delivery, where the operation had been done for a complication of pregnancy, or an accident of labor, or even in some cases of contracted pelvis.

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121 EAST SIXTIETH STREET

1840 GRAND CONCOURSE

1229 CLAY AVENUE

MATERNAL AND INFANT MORTALITY RATES IN 1943

State of Alabama Maternity Clinic Rates, Compared With State Rates as a Whole

WILLIAM A. CUNNINGHAM, M.D., MONTGOMERY, ALA.
(From the Department of Maternal Health, Department of Public Health)

	STATE	WHITE	COLORED
Total births	75,563	48,542	27,021
Stillbirths	2,278	1,140	1,138
Total live births	73,285	47,402	25,883
Clinic Patients:			
Total births	8,764	1,121	7,643
Stillbirths	223	19	204
Total live births	8,541	1,102	7,439
Nonclinic Patients:			
Total births	66,799	47,421	19,378
Stillbirths	2,055	1,121	934
Total live births	64,744	46,300	18,444

12 per cent of all maternity patients attended state clinics.

2.3 per cent of white maternity patients attended state clinics (1 out of 40).

28 per cent of colored maternity patients attended state clinics (3 out of 10).

Seven times as many colored as white attended clinics.

Approximately 70 per cent of the colored are delivered by midwives; in Montgomery County—95 per cent.

Approximately 90 per cent of the colored are delivered at home.

In rural Alabama over 80 per cent of the colored are delivered by midwives and 97 per cent at home.

STATE AS A WHOLE (NUMBER AND RATE)

	TOTAL		WHITE		COLORED	
	NO.	RATE	NO.	RATE	NO.	RATE
Maternal mortality (per 10,000 total births)	228	30.2	111	22.9	117	43.3
Neonatal mortality (per 1,000 live births)	1,917	26.2	1,114	23.5	803	31.0
Stillbirths (per 1,000 total births)	2,278	30.1	1,140	23.5	1,138	42.1

COMPARISON OF THE RATES OF NONCLINIC WITH CLINIC PATIENTS, STATE OF ALABAMA AS A WHOLE

	NONCLINIC			CLINIC		
	TOTAL	WHITE	COLORED	TOTAL	WHITE	COLORED
Maternal mortality	31.3	22.8	52.1	21.7	26.8	20.9*
Neonatal mortality	27.6	23.8	31.8	15.0	10.9*	15.6*
Stillbirths	30.8	23.6	48.2	25.4	16.9*	26.7

*Specially outstanding.

Of special import are the following deductions:

1. Total clinic rates are greatly lower than nonclinic rates in all three categories: a 31 per cent reduction in maternal mortality, a 36 per cent reduction in neonatal mortality, and an 18 per cent reduction in stillbirths.

2. In nonclinic patients, the colored rates are double the white rates in maternal mortality and stillbirths, and 34 per cent higher in neonatal mortality.

3. The colored clinic rates are below the total state rates in all three categories: in maternal mortality by 30 per cent, in neonatal mortality by 40 per cent, and stillbirths by 12 per cent.

4. If we take the two opposite extremes economically and educationally, namely the white private (nonclinic) patient and the colored clinic patient, it is rather startling to find that the colored rate is lower than the white in maternal mortality by 9 per cent and neonatal mortality by 35 per cent; but higher in stillbirths by 13 per cent, probably in the main because of the prevalence of syphilis in the colored.

5. The colored clinic rates are tremendously below the colored nonclinic rates; in maternal mortality by 60 per cent, in neonatal mortality by 51 per cent and in stillbirths by 45 per cent.

6. The white clinic rates are lower than the white nonclinic rates terrifically in neonatal mortality—54 per cent and in stillbirths—28 per cent, apparently because of better supervision of nutrition and syphilis in the mother and infant. Private physicians do not all take serologic tests for syphilis. The maternal mortality rate for white clinic patients however was above that for nonclinic patients by 17 per cent which is understandable since more of them are delivered by midwives, and more home deliveries occur. The economic, educational and social status of the clinic patient is definitely lower than the private patient, and her delivery and aftercare is poorer.

7. As a continuance of Item 2, if we compare colored rates with white in clinic patients, we find the colored rate lower by 22 per cent in maternal mortality, but higher by 43 per cent in neonatal mortality and 58 per cent in stillbirths. The first finding is difficult to explain but the answer to the latter two probably lies again in the prevalence of syphilis in the colored, plus their background of economic and educational inferiority.

8. Although in 1943, there were slightly better than five white births in Alabama to every three colored births, the absolute number of maternal deaths and stillbirths were almost identical. In neonatal mortality however, the colored were almost 30 per cent lower which is more in proportion.

MATERNAL MORTALITY, INFANT MORTALITY, NEONATAL MORTALITY AND STILLBIRTH RATES

STATE OF ALABAMA—1938, 1940, 1942 AND 1943

	TOTAL				WHITE				COLORED			
	1938	1940	1942	1943	1938	1940	1942	1943	1938	1940	1942	1943
Maternal mortality (per 10,000 total births)	63.0	58.8	38.6	30.2	51.1	39.7	27.4	22.9	82.9	89.0	57.3	43.3
Neonatal mortality (under 1 month) (per 1,000 live births)	36.3	38.3	30.5	26.2	32.0	33.0	26.6	23.5	44.2	47.3	37.4	31.0
Infant mortality (under 1 year) (per 1,000 live births)	60.6	61.3	50.1	--	53.5	51.1	40.7	--	72.5	77.9	66.4	--
Stillbirths (per 1,000 total births)	40.2	38.4	31.9	30.1	28.3	28.0	--	23.5	59.5	54.8	--	42.1

COMPARATIVE STATISTICS—1940 TO 1943

TOTAL RATES	MATERNAL MORTALITY	NEONATAL MORTALITY	STILLBIRTHS
1940	58.8	38.3	38.4
1941	49.6	36.0	37.6
1942	38.6	**30.5**	31.9
1943	30.2	26.2	30.1
Overall Reduction	49%	32%	22%

1943 STATISTICS

12 per cent of all maternity patients attended state clinics; seven times as many colored as white attended clinics.

There were 75,563 total births: white—48,542, and colored—27,021. Live births—73,285: white—47,402, colored—25,883.

There were 2,278 stillbirths: white—1,140, and colored—1,138.

Patients attending maternity clinics—8,764 total births: white—1,121, and colored—7,643.

Correspondence

To the Editor:

The long, bloody, tragic history of accouchement forcé has been noted in many obstetric chronicles. More urgently, the nightmarish effects of the procedure are sharply etched in the minds of a still living generation of obstetricians.

A happily forgotten method, it was disinterred in 1929 by Delmas, whose sole modification resided in the fact that he carried it out under spinal anesthesia. As might have been anticipated, Delmas' idea fell rapidly into disrepute and perhaps the obstetric world breathed a great sigh of relief.

Within the last year or two manual dilatation of the cervix under spinal anesthesia (as an elective measure to terminate pregnancy before the onset of labor) was again revived and championed by two surgeons, Koster and Perrotta. (See the 1943 Yearbook of Obstetrics and Gynecology.) It was my good fortune to have had a long conference with Koster concerning the technique he employed. After discussing the method with him, I obtained permission to employ it on the service at Harlem Hospital in a series of cases.

Our experience finds us in wide disagreement with Rosenfeld who reports five cases in the May issue of the JOURNAL: Vol. 47, No. 5, pp. 699-702. We are more interested in at least one statement made by Rosenfeld than we are in the five very interesting cases he presents. On page 701 he states, "It can be demonstrated pharmacologically and certainly clinically that spinal anesthesia relaxes the cervical muscles so that the cervix can be easily dilated, and at the same time, it causes contraction of the corporeal muscles."

Before advancing to pharmacologic or clinical demonstration perhaps an anatomical and histological study would be of value. For example: what are the "cervical muscles"? How do they differ histologically from the corporeal muscle? Are there muscles in the cervix at term or are there merely some muscle fibers? What is the innervation of the cervix? Is there a nerve distribution so arranged that the spinal anesthesia produces the almost incredible effect attributed to it? Why should the muscle fibers in one portion of an organ relax when the tonus of fibers in another portion of the same organ increases? What is the mechanism? Is it possible to efface the cervix manually? These are some of the questions which arise out of theoretic consideration of the method.

From actual utilization of the technique as described by Koster and Perrotta, we have drawn certain conclusions which we have listed dogmatically below. We departed from their technique in that we used 100 mg. of procaine rather than 150 mg. We reduced the dosage because they informed us that they used the larger dosage only out of habit.

From the experiences of Dr. Kassebohm and myself, we feel that the following conclusions are fairly drawn: 1. There is no change in the consistency of the cervix following spinal anesthesia. 2. Where the cervix is completely effaced, there is no change in the consistency of the tissues which bound the os. 3. There is no notable difference in manual dilatation relating to the type of anesthesia. 4. Manual dilatation may be performed under general inhalation anesthesia, presacral block, caudal analgesia, intravenous anesthesia or spinal anesthesia. 5. Rapidity of dilatation results from the dexterity of the operator and the fortuitous elasticity of the cervix; the type of anesthesia has no bearing. 6. With no twinge of conscience and no apology, a too often unremembered cliché must be stated, i.e., manual dilatation means manual laceration.

In such unusual instances as reported by Rosenfeld, rapid delivery by accouchement forcé may be indicated. Rosenfeld warns of the dangers of the procedure and calls for expert attendants. Unfortunately the method may, and to our knowledge, already has reached hands which cannot be so classified. Further it has been used, not in the rare emergency but as an elective procedure to guarantee painless labor. There is no point in listing the dangers attached to such foolhardiness.

Accouchement forcé has too often been life giving and death dealing. Spinal anesthesia has not altered its basic aphysiologic character. It were better that it again be interred and this time its grave firmly and forever sealed lest it again force the opening of graves for mothers. Obstetric art and obstetric conscience will grow without it and the latter will rest more easily.

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NEW YORK, N. Y.
MAY 31, 1944

To the Editor:

For a number of years I have been impressed by the lack of an adequate descriptive term of the patient who calls on the members of our specialty to discover why she has not borne children. The terms "sterile," "barren," and "childless" have been neither scientifically accurate nor esthetically acceptable. "Sterile" and "barren" convey implications which, conventionally and historically, are uncomplimentary and condemnatory. "Childless" is equally indefinite.

I am sure that other members of the specialty have experienced the same reaction with regard to these terms, because I have talked with many of them. The result is that I have been trying to find a term that described the patient who has not borne children, although exposed to normal marital relations over a reasonable period of time, and who now seeks to find the reason.

I have enlisted the aid of Professor (Dean) John C. Bailey, Jr., of Davidson College, a man of no little renown in the matter of language research, and he has come forward with what seems to me to be a practical answer. He suggests the noun "agennesis" and "agennetic" as the adjective. According to this authority, all the necessary descriptive needs are contained in these two words.

He calls attention to the following two points: first, both of these words are spelled with two n's; second, the noun "agennesis" is accented on next to the last syllable, and the "e" in that syllable is long, as in "we."

I would, therefore, request space in your JOURNAL for this proposed addition to our gynecologic and obstetric nomenclature, and thereby at least bring the matter up for discussion, and perhaps a still better term may be discovered.

OREN MOORE, M.D.

CHARLOTTE, N. C.
APRIL 20, 1944.

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Ferris, D. O., and Dockerty, M. B.: Adenocarcinoma of the Body of the Uterus Arising From a Benign Endometrial Polyp: Report of Case, Proc. Staff Meet. Mayo Clinic **19:** 133, 1944.

The authors present a case report dealing with an endometrial polyp which became the source of an adenocarcinoma of the body of the uterus. The authors point out that such a transformation is extremely rare and must fulfill certain criteria such as:

1. The carcinoma must be confined to one portion of the polyp.
2. The base of the polyp must be benign.
3. The surface of the endometrium around the base of the polyp must show no malignant change.

Their case report fulfills the recognized requirements.

JAMES P. MARR

Morton, Daniel G.: Carcinoma of the Uterine Cervix: Prognosis and Treatment, West. J. Surg. **52:** 1, 1944.

Radiation holds first place in the treatment of cervical carcinoma; however, the author believes that surgery still has a limited field of usefulness. Until 1931, the cases at the University of California were treated by radium in the smaller dosage of that day and only occasionally was x-irradiation used for metastasis or extension. Now the x-irradiation is carried up to 3,000 or even 4,000 roentgens. It is believed to be an essential and indispensable part of the therapy not only for its effect upon the primary lesion and the area of primary spread. Roentgen irradiation is not a benign procedure, however. It precipitated death in 18 of the 374 cases here reported. Vascular changes, fibrosis, bone necrosis, and ischemic ulceration of the bowels are a few of the complications encountered.

The treatment plan used by this author is described. Four thousand, five hundred milligram-hours of radium are given in three doses at weekly intervals; 3,000 milligram-hours in the cervicouterine canal and 1,500 milligram-hours in a placque across the cervix. The author has a mild preference for x-irradiation completed about three weeks before the use of radium, but he has used them concurrently and even reversed the sequence without a great difference in results. The advantage of x-irradiation first is that a large, fungating mass can be reduced; and perhaps more important the sloughing cervical mass which is always septic can be cleaned up. Reirradiation is not recommended, the incidence of slough is high and the results are not improved. All therapeutic effect is attained in the initial course of treatment.

Comment is made upon 100 Wertheim operations performed in this clinic for early Schmitz Stage I and II carcinoma. Prognosis in carcinoma of cervix is reasonably good, a hopeless attitude is not justified. The clinical stage of the disease and its immediate response to treatment are the best guides to prognosis.

WILLIAM BICKERS

Cesarean Section

Lull, Clifford B., and Ullery, John C.: Cesarean Section Under Continuous Caudal Analgesia, J. A. M. A. **142:** 90, 1944.

The authors report their observations on 50 cases operated upon at different institutions. Contraindications to the use of caudal anesthesia are enumerated, and the mental preparation of the patient to the procedure is stressed. It has not been used in cases of placenta previa. Barbiturates are given the night before and one hour before the operation. Fifty mg. of ephedrine hydrochloride are given to the patient if the blood pressure is below 140 mm. systolic. In hypertension cases, it is withheld unless the blood pressure falls to 100 mm. systolic. The technique of administration is outlined. Metycaine was used in all cases. None of the babies needed resuscitation. The average estimated blood loss was 100 c.c., the patients are greatly benefited by the administration of morphine and scopolamine immediately after abdominal section or vaginal delivery.

WILLIAM BERMAN

Zecena, Arturo: A Manipulation to Extract the Fetal Head in Low Cesarean Section, Obst. y ginec. Latino-Americanas **1:** 356-358, 1943.

The author comments that manual extraction of the head during cesarean section has been mentioned by other authors, but without details. The following procedure has been used successfully in 15 successive cases.

The operator, standing to the left of the patient and facing her feet, carries out the manipulation with the right hand. With a movement of forced pronation, he turns the palm of his hand so that it is facing the face of the patient. He introduces the fingers with the exception of the thumb between the left border of the uterine incision and the fetal head. Taking a step forward, in order to increase the extension of the arm, by movements of flexion of the fingers, he turns the fetal head until it lies on the palm of his hand. If necessary, an assistant exerts pressure deeper in the uterus at the proper moment, to aid in the expulsion.

This manipulation is easily carried out and does not present the difficulties of other procedures (increase of diameter of the fetal head, injury, infection, etc.) and, hence, is recommended by the author.

J. P. GREENHILL

Perez, M. L., and Echevarria, R.: Intraperitoneal Sulfanilamide Treatment in Cesarean Section, of Infected Cases, An. Inst. de Mat. y Assist. Soc. **4:** 9-18, 1942.

The authors have used sulfanilamide intraperitoneally in cases of the low cervical cesarean section where contamination of the peritoneal cavity would have followed operation. The amounts used were large, never less than 6 to 8 mg. and this level was maintained for 3 or 4 days. In 11 previously reported cases, there was no peritoneal infection but there was one death. This was proved to be due to sulfanilamide poisoning and followed the instillation of 8 Gm. of sulfanilamide intraperitoneally.

J. P. GREENHILL

Endocrinology

Borras, P. E.: Possible Hormonal Effect of the Endometrium on Ovary of Hysterectomized Animals, An. Catedra de clin. ginec. 2: 104-107, 1943.

Such an effect is suggested by the author on the basis of experiments in rabbits which received injections of the lipoid fraction of extract of endometrium. The experiments showed that uterine extracts exert a demonstrable action on the ovary, which corroborates the uteroovarian hormonal correlation. They suggest clinical trial of uterine extracts, so far not investigated, in the treatment of glandular insufficiency in women.

Although these experimental results have been duplicated by other workers, the author advances a word of caution regarding interpretation of these results. He points out that extracts of the endometrium contain a considerable quantity of estrogenic substances and that the results obtained may be nothing more than the effect of these substances, rather than a supposed endocrine capacity of the endometrium. Numerous experiments to test this hypothesis have been devised and partially accomplished, and none of the evidence so far accumulated tends to indicate that the results are due to estrogenic substances. Hence, the author believes that endometrial extracts act in a very specific way, without any relation to their possible estrogenic effect.

J. P. GREENHILL

Belizan, L. A.: Treatment of Certain Female Sexual Disorders by Transplantation of the Pituitary, An. Catedra de clin. ginec. 2: 213-233, 1943.

The author reports a second series of thirteen cases in which the technique of hypophyseal implantation was modified slightly from that generally used, and which he had employed in an earlier series of eleven cases.

Patients were chosen with a general or ovarian disturbance which could be regarded as secondary to a primary pituitary deficiency. Most of the patients had not responded satisfactorily to other types of treatment. Only one implantation was made, with no other treatment to supplement it, in order to determine categorically whether this procedure is efficacious and if so, to determine the duration of its effect.

In some patients, an effect was produced which lasted approximately four months and in others, there was no effect. In the first series, the most definite effect seemed to be in connection with libido and the orgasm, but these were not improved in any patient in the second series. On the other hand, there were many menstrual changes; oligomenorrhea and hypomenorrhea were benefited especially, although the benefit was distinctly temporary.

J. P. GREENHILL

Caso, F. C.: Endocrinology and Stomatologic Practice, Gac. méd. de México 73: 409-415, 1943.

In hyperthyroidism, sometimes several teeth are present at birth; caries are frequent from lack of calcium; the superior maxillary bones are fragile; and there is increased salivation. In hypothyroidism, characteristic changes include: delayed dental development, large central incisors, small lateral incisors, overlying teeth, congenital malformations of the mouth and teeth, malocclusion, chronic infection of the tonsils and chest, enamel and dentine abnormally soft, radicular reabsorption, decreased density of the crowns, decalcification of the bones of the wrist and of the superior maxilla, hypertrophic tonsils and dry mouth.

In pituitary hyperfunction, there may be early eruption, large teeth of square type, wide superior incisors widely spaced, with errors of alinement, teeth resistant to caries, marked mandibular hypertrophy. With hypopituitarism, common changes are late eruption, small mandible (overbite), small, infantile teeth, flattened canines, rapid caries, crowded teeth, teeth of bluish tint, possible pyorrhea.

In hypertrophy of the thymus, there are delayed eruption, small upper maxilla, large central incisors, flattened lateral incisors, poor enamel, extensive caries, congenital malformations of the mouth and upper and lower jaws, hypertrophied tonsils and glands, and pyorrhea. With diabetes, there is early eruption, extensive caries, granulomas, inflammation of the edges of the tongue, abscesses and fissures of the tongue, gingivitis and ulcerations, pyorrhea, stomatitis, dry mouth, increased cholesterol in the saliva, acrid and metallic breath.

In hyperadrenalism, early eruption and very large canines are noted. With hypoadrenalism, the teeth are yellowed, and there are many dark spots on the mucous membrane. With hypergonadism, frequent caries and early loss of the teeth are characteristic. In hypogonadism, the lateral incisors and canines are flattened, and this condition may have a causal relationship to pyorrhea. In pregnancy, there are caries through loss of calcium, as well as change of color of the teeth, hypertrophy of the gums, gingivitis and paresthesia of the oral mucosa.

In hyperparathyroidism, changes include decalcification of dentine, with frequent caries and difficult preparation of cavities for fillings, radicular infection, and mandibular giant-cell tumors. In hypoparathyroidism, there are atrophic teeth in cradle form, defective enamel, lateral erosion of teeth, horizontal cracks and furrows of the enamel, and a possible connection with pyorrhea.

The author concludes that the endocrinopathies have marked repercussions in the mouth, and once these are recognized, the dental surgeon can collaborate with the physician in treatment. He points out that pyorrhea is not a pathologic entity, but a syndrome related to endocrine dysfunction; thus the infectious theory is superseded. The microorganisms (nonspecific in this case) develop at a site of least resistance, but the cause of dental decalcification should be sought in the body, and especially in the glands of internal secretion.

J. P. GREENHILL

Bishop, P. M. F., and Folley, S. J.: Implantation of Testosterone in Cast Pellets, Lancet 246: 434, 1944.

The authors, for over a year, have been studying, with reference to ghost formation, the absorption of cast and compressed pellets of steroid hormones implanted for clinical purposes in human subjects.

The writers implanted 100 mg. pellets of testosterone into male subjects. These were removed, reweighed and quantitatively extracted with ether. No evidence of ghost formation was demonstrable in the interior of the pellets. There was also a satisfactory agreement between the experimental determinations and theoretical curve indicating that the in vivo absorption rate of a cast pellet at any instant is proportional to its surface area, allowing for the conclusion that encapsulation, which was observed in most cases, has no progressive retarding effect.

The initial absorption rate of the authors' implanted pellets was approximately 1.1 mg. per day, but by 50 days this had been reduced by a third. Cast pellets were absorbed faster (12 per cent greater) than the compressed pellets. This phenomenon is explained primarily by the greater surface area of the cast pellets. The twenty determinations of the authors illustrate most succinctly their conclusions.

C. E. FOLSOME

Extrauterine Pregnancy

De Queiroz, Alicio Peltrier: Advanced Ectopic Pregnancy, An. brasil. de ginec. **7**: 193-202, 1942.

According to the author, advanced ectopic pregnancy is one that has progressed beyond the fourth month. Some of these cases may progress to term and a live fetus be extracted. The chances of survival are, however, very slim for most of these fetuses present deformities incompatible with life. In other cases, whether or not the pregnancy has reached term, the fetus dies after "false labor," and is retained as a fetal cyst. The contents of an aseptic fetal cyst may undergo various changes like mummification, skeletization, saponification, calcification, etc. The ovum may, however, become infected, causing suppuration with all its sequelae, including peritonitis and death. On the other hand, in some cases, this suppuration of the cyst may lead to a spontaneous cure, in that the cyst perforates into the bladder, rectum or through the abdominal wall.

The first of the two cases dealt with in the present communication was that of a woman, aged 34, para vi, who became pregnant two years previously, carried the pregnancy to the eighth month, and was found on operation, at the twenty-fourth month, to have an intraligamentary fetal cyst. Because of technical reasons, a supravaginal hysterectomy with removal of both adnexa was performed. The second case was that of a woman, aged 34, in whom pregnancy likewise progressed until the eighth month, the operation being performed at the twelfth month. This consisted of sectioning and emptying the cyst with partial removal, after separation of adhesions which fixed the cyst to the mesosigmoid and to the Douglas pouch. Both patients showed uneventful recoveries.

J. P. GREENHILL

King, Samuel L.: Coexisting Intrauterine and Extrauterine Pregnancies, New England J. Med. **229**: 965, 1943.

The author presents a case report dealing with coexistence of intrauterine and extrauterine pregnancy.

No extrauterine mass was palpable preoperatively, but signs and symptoms of intraperitoneal hemorrhage and a suspected ectopic gestation led the surgeon to perform a laparotomy. A bilateral salpingectomy and appendectomy were performed. The intrauterine pregnancy continued to near term.

JAMES P. MARR

Gynecology

Araya, R.: Fundamental Concepts of Ovarian Histophysiology, An. Catedra de clin. ginec. **2**: 30-68, 1943.

The author presents a histologic study of 50 ovaries removed from patients aged 20 to 40, correlated with the menstrual cycle. A previous study had shown no correlation between ovulation and menstruation, i.e., ovulation was demonstrated to occur at any time during the menstrual cycle.

These careful microscopic studies of all elements of the ovary confirm the concept concerning the development of hormonal function of the ovary. Development of the hormonal functions is intimately related, on the other hand, to the activities of the entire body, especially to those of other endocrine glands, particularly the pituitary.

Various organs of the body participate in the menstrual process, transporting by way of the circulating blood elements indispensable to regular development of its essential functions, related to reproduction and preservation of the species. The

anterior hypophysis is especially important, which by means of a follicle-stimulating hormone (gametotropic) and a luteinizing fraction (hormonotropic) stimulates the hormonal activities of the ovary, which, by means of its estrogenic-folliculin and luteinizing-progesterone secretions causes changes in the endometrium which lead to menstrual loss when the ovum has not been fertilized. Participation of the entire body and of particular organs in the menstrual process is evidenced by trophic and functional disturbances of the genital apparatus, produced in the course of illness. Among the former are atrophy and hypertrophy of the genitalia; and the latter are manifested by anomalies of menstruation.

The literature abounds in examples, outlining effects of chronic diseases, intoxications, blood diseases, and of diseases of various organs, such as the heart, kidneys and of endocrine diseases, affecting the pancreas, thyroid, adrenals, and of vasomotor disturbances, or diseases of the autonomic, or central nervous systems.

The author includes a graphic presentation of four successive menstrual cycles, in which the ovum was formed in only three, and these at different periods of the cycle, notwithstanding the fact that the cycle was in all instances completely normal. This is because the menstrual process is the result of integral activities of the ovary, within which a prominent role is played by the development of numerous primordial follicles which tend toward atresia, and among which only one or two may be transformed into Graafian follicles, which in turn may or may not develop into a mature ovum.

J. P. GREENHILL

Ahumada, J. C., Chevalier, R. M., and Sammartino, R.: Actinomycosis of the Ovary, Bol. Soc. de obst. y ginec. de Buenos Aires **22**: 362-370, 1943.

The patient, a single woman, aged 24, first had acute symptoms in the abdomen, localized in the right lower quadrant, which were interpreted as appendicitis. Successive laparotomies marked a serious surgical course which caused her death three years later, despite combined therapy employed to combat the infection.

The infection can reach the genital organs through the ascending, or intracanalicular route; the hematogenous, with metastases; and the entral, that is the rectosigmoid or cecal, favored by scant peristalsis, cecal stagnation and mucous microtrauma. From this site, it spreads by the intraperitoneal route through adhesions, or extraperitoneally through the peritoneum connecting with the ovaries. Actinomycosis of the ovary may be primary, i.e., confined to the genital apparatus; diffuse throughout the whole system (80 per cent); or enclosed (?) actinomycosis, localized in a pre-existing genital cystic lesion.

The lesion consists of hard callus, pierced with numerous cavities filled with pus; this explains the progression and diffusion, and the tendency to extend to the Retzius cavity, the retroperitoneum, the iliac fossae, perineum, or abdominal skin, and even to neighboring organs, the rectum, bladder and vagina.

The symptoms do not form a clinical cavity: the disease may begin with acute abdominal symptoms, in an incipient form, or even without symptoms, until it is diagnosed as a tumor. With progression, there are various types of pain, febrile reactions, symptoms of colitis, with alteration of the sexual cycle only in the final stages. Progression is interspersed with apparent remissions, purulent fusion and secondary fistula formation, invasive tendency, abscess formation with but slight healing of the cavities, and a tendency to new fistula formation with invasion of the zones mentioned.

Definite diagnosis depends on histologic study and isolation of the organism. The prognosis is extremely serious, with cures reported ranging between 10 and 40 per cent. In the treatment there are three procedures: surgery, roentgen therapy and chemotherapy with iodine and arsenical preparations, and in some instances specific vaccine. Their efficacy is dependent on early diagnosis and limitation of the lesions.

J. P. GREENHILL

De Moraes, A.: War Trauma and the Female Genital Apparatus, An. brasil de ginec. **8:** 283-294, 1943.

Due to the type of war now being fought, everyone may be injured by air bombardment. The author presents the following outline of the ways in which war trauma may effect the female genital apparatus.

I. By direct action on the genital apparatus
   1. In pregnant women
   2. In nonpregnant women
      a. Normal genital tract
      b. Pathologic genital tract

II. Repercussion on the female genital apparatus and its functions by traumatic agents acting at a distance
   1. By physical action (displacements of the body)
   2. By action on the vegetative nervous system (emotion)

III. Skeletal lesions with primary and secondary effects on the bones of the pelvis affecting the reproductive process.

J. P. GREENHILL

Chevalier, R. M., and Salaber, J. A.: Chorionepithelioma: Diagnostic and Therapeutic Considerations, Obst. y ginec. Latino-Americanas **1:** 471-478, 1943.

The authors suggest after a thorough review of the literature, that the diagnosis of chorionepithelioma should be accomplished in three separate steps; clinical, anatomic, and biologic. The clinical symptoms depend on localization, whether or not there is a coexistent normal or pathologic pregnancy, and the presence or absence of metastases. The degree of malignancy also accounts for much variation in symptoms. In intracavitary uterine chorionepithelioma, the classic triad of symptoms consists of recurring metrorrhagia, serous discharge from necrosis of the tumor, and fever, indicating infection or thrombosis in an anemic patient, with transparent pallor and ash color, and with albuminuria and cylindruria. Examination reveals a globular uterus, smooth, soft, movable, with a softened cervix. Sometimes the cervical orifice is open, permitting intrauterine palpation. Intramural chorionepithelioma is asymptomatic until it perforates the endometrium or perimetrium. When the lesson is situated in the cervix, the significant finding is repeated metrorrhagia which does not respond to curettage, whose true nature finally is revealed by histologic study or metastases.

The clinical examination is completed with hematologic and radiographic studies, and then histologic study of material from the cervical or intrauterine cavity is made. Interpretation is somewhat difficult, because the elements constituting the tumor are morphologically and biologically identical with cells derived from the trophoblast, giving rise to doubt as to whether they are from a chorionepithelioma, or from ovarian rests. The following are considered as presumptive indications of chorionepithelioma: (1) Marked solid proliferation of the chorial epithelium; (2) existence of changed maternal tissue when deep portions are obtained.

Biochemical investigation yields confirmatory evidence of the presence of chorionepithelioma, which usually is accompanied by excessive gonadotropic hormone, although some negative tests have been reported. The authors believe the value of biologic determinations lies in serial tests and in correlation with clinical and pathologic findings.

The plan of treatment in a patient with chorionepithelioma should be: (1) Complete clinical study; (2) investigation of metastases; (3) surgical treatment by the abdominal route, permitting complete examination of the genital organs, finding the exact situation of the tumor, and, in removing it, reducing uterine trauma to a minimum with ligation of the veins to prevent operative embolism; (4) in ac-

cordance with the extent of the lesion and the patient's age, total hysterectomy, or subtotal, with the possibility of saving the adnexa; (5) roentgen therapy for visceral metastases; (6) vaginal surgery and radium for vaginal metastases.

J. P. GREENHILL

D'Aquila, H. P.: Erythrosedimentation in Complicated Myomas, An. Catedra de clin. ginec. **2:** 251-258, 1943.

The author discusses this subject with details from nine illustrative cases. She believes that a high sedimentation rate in the presence of uterine fibromyoma (eliminating other causes for this finding) is a definite indication of a complicated lesion, even though gynecologic examination may not reveal any abnormality. Histopathologic study should always be carried out after operation for removal of a myoma accompanied by high sedimentation rate. This will reveal areas of tissue showing necrobiosis, hyaline and mucous degenerations, localized infection, and sometimes sarcomatous and carcinomatous zones. Circulatory changes constitute approximately 30 per cent of the complications in uterine myomas.

J. P. GREENHILL

Lavarello, A. G.: Central Abscess of the Ovary, An. Catedra de clin. ginec. **2:** 272-288, 1943.

Central abscess of the ovary and abscess of the corpus luteum are, from the anatomopathologic standpoint, two distinct processes. The former, surrounded, that is, within the elements of the organ, causes profound changes both in function and structure; there are progressive stages, from normal tissue to total destruction of the ovary, at whose expense the purulent cavity is formed. In an abscess of the corpus luteum, the process may be called peripheral, and there is not destruction, but alteration, usually of the infiltrative type, of the parts of the ovary adjoining the process.

Most authors regard the pathogenesis of central abscess as of puerperal origin, either post partum or postabortive, and from his observations, the author is inclined to agree.

In regard to classification, the author suggests that, on an anatomopathologic basis, central abscess should be included in chronic interstitial oophoritis, while luteal abscess belongs to the acute types of ovarian inflammation due to peripheral infection.

J. P. GREENHILL

Bates, Robley, Jr., and Rucker, Pierce M.: Tuberculosis of the Vulva, Virginia M. Monthly **71:** 199, 1944.

Tuberculosis of the vulva is the rarest form of genital tuberculosis. It must be differentiated from esthiomene, tertiary syphilis, granuloma inguinale, and carcinoma. The vulval lesion may be either primary or secondary, the former being rare and difficult to prove conclusively. That it may be acquired by local inoculation at coitus is open to question, but it is true that the disease has been produced in the vagina of guinea pigs after first sensitizing the animals. In the secondary cases, the infection often extends from a neighboring organ such as bladder or rectum, and of course, may result from a descending infection from the vagina or uterus.

Prognosis must be guarded, spontaneous healing sometimes occurs. The treatment is not well established, but cases are cited from the literature treated by excision, radiation, or local application of zinc chloride in alcohol.

The authors report a case of secondary vulval tuberculosis with a history of pulmonary tuberculosis in 1935, a history of rectovaginal fistula in 1932. At the

age of 44, she reported for examination, not for the ulcer on her vulva, but to see if she was pregnant. A photograph of the lesion is shown together with the photomicrograph of the tissue removed for biopsy. The base of the ulcer was granular and bathed with pus, it was acutely tender. The genitals were otherwise negative. The pathologist reported "nests of epithelioid cells situated just below the epithelium and surrounding giant cells of the tuberculous type." Although acid-fast stains could not be done, the histologic findings were characteristic of tuberculosis.

No treatment was instituted because of the patient's extreme pulmonary involvement. She died a few months after the local lesion was discovered.

WILLIAM BICKERS

Gynecologic Operations

Borras, P. E.: Obstruction of the Bladder Neck in Women, An. Catedra de clin. ginec. 2: 130-156, 1943.

Two cases are reported by the author with discussion of symptoms, endoscopic signs, pathologic anatomy and treatment. The outstanding symptom is painful and difficult urination. Occasionally, there is some hematuria and urinary retention. Following the local symptoms, general disturbances result from lack of rest, distracting pain, inability to work, and increasing nervousness, which is exaggerated with the failure of all medical treatment. The cystoscopic picture is characterized by thickness of the vesical columns and cells, and sometimes by true diverticuli, which reflect the pressure to which the bladder musculature has been subjected because of the obstruction at the outlet due to rigidity of the sphincter. The muscular coat of the sphincter, histologically, shows, marked hypertrophy and hyperplasia of the fibers, changing their disposition into a picture resembling uterine myoma. Within the muscular tissue, infiltration of inflammatory elements may be found, and always a sclerotic process which leads toward fibrous transformation of these elements of the bladder neck.

Once the diagnosis of disease of the bladder neck has been made, there is only one treatment and that is surgical. It is necessary to open the bladder neck itself, and three routes may be utilized, perineal, endourethral or vaginal, and transurethral. The sclerotic portion of the bladder neck is destroyed through a resectoscope, preferably, the MacCarthy instrument, because it allows vision of the surgical field, and extensive areas of tissue can be resected rapidly, because of the variation in form and size of the electrodes. The two patients reported were operated by the transvesical route, because a MacCarthy resectoscope was not available at the time, and the transurethral route promised to be difficult because the bladder in both instances could stand little distention. Marion prefers the transvesical route in all cases because it allows complete and radical operation without increasing the risks, and because it permits exact calculation of the zone to be extirpated, and even allows complete removal of the bladder neck. The author, however, notwithstanding the good results in his two cases with this method, believes that, generally, the transurethral approach is the one of choice.

J. P. GREENHILL

Borras, P. E.: Morbidity and Mortality in Surgical Treatment of Uterine Tumors, An. Catedra de clin. ginec. 2: 90-96, 1943.

The author presents a statistical study of 1,240 cases representing a 30-year experience on two surgical services. In the majority of instances (968), the tumors were fibromyomas; in only 22 cases was cancer present with the fibromas. The predominant symptom was menorrhagia or metrorrhagia in 687 cases (54.83 percent). In 663 instances, another operation, such as appendectomy, salpingectomy, etc., was performed concomitantly.

Postoperative complications occurred in 346 of the 1,240 cases, the majority caused by pulmonary processes (38.72 per cent). In order of frequency were the following: phlebitis, paralytic ileus, parotitis, cystitis, surgical shock and fever of undetermined cause. Cardiovascular complications included collapse, peripheral failure and cardiac insufficiency.

Of 139 patients who had total hysterectomies, 108 had some postoperative disturbance. Among 769 cases in which subtotal hysterectomy was performed, complications occurred in only 95. In reviewing the record of complications in recent years, it is obvious that newer methods of preparing patients for surgery and recent pathogenic concepts of certain complications facilitate prevention and treatment of all postoperative difficulties. This study indicates that the index of mortality has decreased constantly and now is not more than 2 to 3 per cent.

In the statistics for the 30-year period, the mortality rate for surgery of the uterine muscle was 7.18 per cent. In contrast to this, in the last five years, it was 1.8 per cent. Nevertheless, it is only fair to recall that formerly patients would submit to operation only in advanced stages, whereas now surgery is carried out much earlier in many cases. Of 1,240 patients in the entire series, 89 died. The greatest number of these deaths was due to cardiac complications (36, or 42.69 per cent). Pulmonary complications accounted for 25.82 per cent of the deaths.

J. P. GREENHILL

Borras, P. E.: Surgical Treatment of Uterovaginal Prolapse, An. Catedra d clin. ginec. **2**: 97-103, 1943.

The author states that no fixed procedure can be followed in operative treatment of vaginal and uterovaginal prolapse, for various factors must be considered: The condition of the tissues, grade of lesion, patient's age, with all its subsidiary factors, constitutional type, economic status, etc. In his experience, there are four fundamental facts to be ascertained: whether or not a retroflexion has to be corrected; whether or not a cystocele requires dissection of the fascia and reefing of the pubovesico-uterine ligaments; whether there is elongation of the cervix; whether a posterior colpocele requires repair, and if so, its extent.

These types of cases are discussed in connection with the Halban and Fothergill operations. The author believes that both are superior techniques, and that the results are practically identical, but for simplicity of technique and minimal risk, he prefers the Fothergill procedure. He comments that his own statistics would seem to contradict this, since he reports two deaths with the Fothergill, and none with the Halban operation. However, one of these patients was aged and died from syncope twelve days after operation, while the other got out of bed, against the surgeon's instructions, and suffered a severe hemorrhage, necessitating removal of the tampon by the attending physician, with separation of sutures and subsequent infection.

Two series of cases from the Hospital Español and the Catedra de Ginecologia are presented, a total of 632. Operation was carried out in 589; the Halban technique was used in 293, and the Fothergill in 145. Sixty-four hysterectomies for prolapse and 28 ward cystopexies were also done, and the remainder of the operations was performed by other techniques or was done before the Halban operation was used.

The surgical results are entirely satisfactory with either the Halban or Fothergill operation. There are practically no recurrences and the patients generally exhibit great improvement. There were only five cases of recurrence after the Halban, and two after the Fothergill. Postoperative complications were: Hematoma of the lateral vaginal wall, 1 case (Halban); hemorrhage, 2 cases (Halban); cystitis, 8

cases (2 Halban, 6 Fothergill); febrile course, 3 (2 Halban, 1 Fothergill); phlebitis, (Halban); cardiovascular failure, 1 (Fothergill).

All types of anesthesia were used, but spinal anesthesia with novocain and infiltration of the vaginal tissues with adrenalin solution was used in the majority.

J. P. GREENHILL

Labor, Complications

Ferrari, R. A.: Present Conception of Treatment of Obstetric Shock, Obst. y ginec. Latino-Americanas **1:** 479-485, 1943.

Obstetric shock is a syndrome resulting from depression of many functions—neuromuscular, glandular and visceral, but reduction of effective circulating volume of blood and of arterial tension is of basic importance, and treatment must be directed toward combating this.

Transfusion of whole blood is the best treatment for patients whose shock results from quantitative loss of blood, and who need both plasma and blood cells. Transfusions of whole blood are contraindicated in patients whose shock is the result of loss of plasma (obstetric operations with prolonged visceral exposure), because of hemoconcentration, and administration of plasma alone is more beneficial.

Blood plasma is the substitute which is now accepted as most satisfactory and effective. It meets the prime necessity of restoring circulating volume promptly. It is physiologic and stable, easily transported and prepared easily and quickly.

As complementary medication are the administration of analeptics with peripheral and central action; warming of the patient; lowering of the head; oxygen and morphine in cases with excitement or pain, intravenous injection of warm saline solution. Heart stimulants are ineffective, as are also subcutaneous or intramuscular fluids, because the peripheral circulation is greatly retarded. Preseverence in treatment and supervigilance of the patient with shock are necessary to obtain satisfactory results in this condition.

J. P. GREENHILL

Macleod, A. J.: Manual Dilatation of Pelvis, Brit. M. J. **2:** 484, 1943.

The author refers to his previous report (1936), of a case in which the pelvic girdle was dilated to avoid the death of a patient in parturition. He now reports four cases. They were primiparas with minor degrees of pelvic contraction, complicated by early rupture of membranes and showed signs of fetal distress after protracted labor and at a time when "the size-relation of the head and passages was unfavorable." He writes with reference to technique: Leverage must be from bone to bone, and may be done with the fingertips on one and the knuckles, or the back of the hand against the other. The pressure should not be long continued—a few seconds, and should move from one pair of points to another. The fingertips may stretch the taut ligaments by stroking across their axis.

The author concludes that manual dilatation of the bony pelvis can be safely and successfully used to minimize birth trauma and that it is especially indicated in cases of slight disproportion which have to be delivered at an unfavorable stage.

FRED L. ADAIR

Item

The Practical Clinical Importance of the Rh Blood Type and a Project for the Collection and Preparation of Suitable Rh Typing Serum

In 1940, Landsteiner and Wiener discovered the new blood type—Rh, present in 87 per cent of the white population and absent in 13 per cent. At first, it was thought to have no practical or clinical importance. However, it was soon demonstrated by Levine and by Wiener that Rh-negative individuals (lacking this Rh agglutinogen) might, under certain circumstances, develop immune antibodies against the Rh factor and suffer serious consequences from the action of such anti-Rh agglutinins.

Abundant evidence has been collected by now to show that anti-Rh agglutinins may be developed in Rh-negative males and females as the result of one or more transfusions with Rh-positive blood, and in women, by repeated pregnancies involving an Rh-positive fetus (this blood type being inherited as a dominant characteristic from the father).

Recognized intragroup transfusion reactions due to Rh incompatibility have apparently been quite rare in civilian practice. This does not imply that Rh-negative individuals who receive Rh-positive blood fail to develop antibodies, in most instances. On the contrary, data from the Blood Grouping Laboratory of Boston suggest that many such recipients develop weak agglutinins. Subsequent transfusion reactions are fairly mild unless numerous transfusions are given and strong agglutinins develop. Probably the most important reason for failure to note a higher percentage of hemolytic transfusion reactions of this type is that multiple transfusions are the exception in civilian practice. More than 95 per cent of the transfusions are single infusions of blood. In contrast to this, in the treatment of members of the Armed Forces, multiple transfusions are exceedingly common, and therefore transfusion reactions in the 13 per cent of the population which are Rh negative are quite likely to become more frequent and severe, thus interfering with benefit from the procedure, with speed of convalescence, and even with eventual recovery. This has been borne out by statistics available from the British Armed Forces.

Because of the increasing availability of plasma and whole blood, and the attempt to diminish maternal mortality due to hemorrhage and puerperal sepsis, transfusions are now given to patients in obstetric services much more often than in days past. In contrast to the experience with medical or surgical cases, a first transfusion of Rh-positive blood to an Rh-negative mother, who has been sensitized by pregnancy with an Rh-positive fetus, may be followed by a fatal reaction. Also an Rh-negative woman of childbearing age, given Rh-positive blood, will be sensitized, develop anti-Rh agglutinins, and if she then has a pregnancy involving an Rh-positive fetus, the child will develop erythroblastosis, often of the most severe type.

To sum up the accumulated facts, it may be stated that Rh incompatibility is of practical importance under the following conditions:

1. Rh-negative recipients, men and nongravid women, who receive repeated transfusions of Rh-positive blood may have intragroup hemolytic transfusion reactions. Such reactions do not occur following the first transfusion, but after a suitable interval for the development of antibodies, further transfusions produce signs of increasing hemolytic reaction with jaundice, anemia, and finally anuria.

2. Rh-positive infants born to mothers who have anti-Rh agglutinins may show varying degrees of hemolytic anemia of the newborn, or erythroblastosis fetalis. The severer forms are characterized by late fetal death with congenital hydrops, and icterus gravis. In this situation, Rh typing of mother, father, and child are of diagnostic value, and demonstration of anti-Rh agglutinins in the mother may fix an otherwise questionable diagnosis.

3. Serious and even fatal hemolytic transfusion reactions may result from the *very first transfusion* in Rh-negative women who have been sensitized and have developed anti-Rh agglutinins through pregnancies.

4. The use of Rh-positive blood for transfusion of Rh-negative women even for the first time may initiate the formation of anti-Rh agglutinins and produce erythroblastosis of a severe or fatal form in their Rh-positive offspring.

For the above reasons, it has become apparent that Rh typing should be carried out for:

1. Recipients of whole blood or of resuspended red cells, especially if multiple transfusions are contemplated, in order to avoid giving an Rh-negative individual blood that is not compatible according to this factor, i.e., Rh-positive blood.

a. It is most important to type recipients of multiple transfusions or persons having a history of previous transfusions.

b. Donors and stored blood should also be typed for Rh, so that suitable blood is available for the Rh-negative individuals.

2. Any woman whose history suggests the possibility of erythroblastosis in the fetus—either by one or more stillbirths, or infants born with hydrops, jaundice, or anemia, before even a first transfusion is given, since a fatal reaction may occur.

3. Women of childbearing age before transfusion, since Rh-negative women given Rh-positive blood may be so sensitized that future pregnancies will result in dead or damaged infants.

4. Babies born with jaundice and anemia, in order that their recovery may be facilitated by transfusion with Rh-negative blood.

The Military Services require Rh-typing serum even more urgently than do the civilian hospitals, since multiple transfusions are so much more common in military institutions, and also because obstetric services are expanding in military establishments. Not only is it necessary to have such serum for the typing of recipients, but also for the typing of prospective donors, either for the Rh-negative patients or for a donors list or for banked blood for emergency use. The most serious difficulty in this connection has been the relative paucity of available serum. The reasons for this are threefold:

1. Experimental or animal serum is difficult to produce and gives agglutinations that are unreliable or difficult to read by the average technician.

2. High-titered serum of human origin occurs chiefly in women recently delivered of erythroblastotic infants, and even here it is found in only one of 20 such women, or one in 4,000 deliveries.

3. Such high-titered serum may be highly specific (70 per cent instead of 87 per cent positive reactions), and therefore may not be useful for general Rh testing. This makes the occurrence of high-titered useful serum about one in 6,000 deliveries.

For these reasons other means of increasing the supply of Rh-typing material seemed required. It had been noted that low-titered anti-Rh serums were much more commonly found (ten times as often) than the high-titered agglutinins. However, this material was not safe for general laboratory use because the tests obtained were not clear-cut and many negative results occurred with known Rh-positive cells. Through the cooperation of the Department of Physical Chemistry of the Harvard Medical School such low-titered serum was concentrated into a globulin fraction yielding good typing results. This opened the possibility of utilizing the more abundant supply of serum containing low-titered Rh agglutinins and thereby possibly meeting the need for Rh-typing material.

Accordingly, a project was started under contract from the Office of Scientific Research and Development of the Committee on Medical Research for the collection and preparation of Rh-typing serum. During the past six months, meetings have been arranged with obstetricians, pediatricians, and clinical pathologists in all the large medical centers, and the facts regarding the need for Rh-typing serum have been presented. It has been suggested that they send a few c.c. of blood on any patient known to them to have had a baby with erythroblastosis or possible erythroblastosis (including late fetal death of undiagnosed cause) delivered within the last two years. If the serum, by in vitro tests, shows a useful amount of anti-Rh agglutinin, the physician is notified and requested to obtain from the patient 100 to 500 c.c. of blood to be shipped promptly. Such material is pooled for concentration of the anti-Rh agglutinin, thereby producing a useful typing globulin. Seventy per cent of the resulting serum is set aside for use by the Military Services, and thirty per cent is credited to the hospitals or physicians contributing in this enterprise. Such a credit can be drawn on immediately in the form of standard Rh typing serum, so that any hospital or laboratory may have its own material without delay. Special preaddressed containers and test tubes are being sent to all physicians and hospitals cooperating in this project so that shipment of specimens may be expedited. Also collecting bottles and preaddressed containers for sending blood serum via air express, collect, are obtainable on request.

Only through such a cooperative enterprise for obtaining large amounts of Rh-typing serum does it seem possible to meet the urgent and increasing needs of the Military Forces, as more whole blood is being used; also by this means it is hoped to supply the immediate and future demands of obstetric and general hospitals.

All requests for information and for material should be addressed to Dr. Louis K. Diamond, Blood Grouping Laboratory, 300 Longwood Avenue, Boston 15, Massachusetts.

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